Validation of clinical tools to measure visual functions in children with cerebral visual impairment

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A thesis submitted as part of the requirement for the degree of Doctor of Philosophy in Optometry and Vision Sciences

(Collaborative research project undertaken from City, University of London, London, United Kingdom and Brien Holden Institute of Optometry and Vision Sciences, L V Prasad Eye Institute, Hyderabad, India)

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Declaration

I hereby declare that the thesis titled, "**Validation of clinical tools to measure visual functions in children with cerebral visual impairment**" is my original work and the thesis has not formed the basis for the award of any other degree. The information derived from the literature has been duly acknowledged in my thesis.

26 March 2024

Rebecca Sumalini Chakram **Date**

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COVID-19 Impact Statement

This statement is provided for the aid and benefit of future readers to summarize the impact of the COVID-19 pandemic on the scope, methodology, and research activity associated with this thesis. The academic standards for a research degree awarded by City, University of London and for which this thesis is submitted remain the same regardless of this context.

1. **Summary of how the research project, scope or methodology has been revised because of COVID-19 restrictions**

   A total of 150 children with cerebral visual impairment (CVI) were planned (pre-pandemic) to be recruited as per sample size calculation, these numbers could not be achieved because of the pandemic. Some of the common concerns reported by parents included difficulty in planning another hospital visit during the pandemic, travel concerns and fear of the child contracting the virus at the hospital.

   In order to recruit children in the control group (age-similar typically developing normally sighted children), the initial (pre-pandemic) plan was to approach play schools and in case of very young children to approach parents bringing their children for regular vaccination at Rainbow children's hospitals, Hyderabad, India. However, this was also not feasible due to the pandemic as schools were closed for a long period of time and there was a decline in the number of children consulting in the hospitals as well. Therefore, the control group were recruited from the local children's home and local church community after obtaining ethics approval.

2. **Summary of how research activity and/or data collection was impacted because of COVID-19 restrictions, and how any initially planned activity would have fitted within the thesis narrative**

   The data collection phase for the study was initiated in October 2020, i.e., post first (complete) lockdown in India. The COVID-19 restrictions were still in place and the public were advised to travel only if it was essential. After getting permission from Rainbow children's hospitals and at L V Prasad Eye Institute (LVPEI), Hyderabad, India, the principal investigator started data collection. The ongoing COVID restrictions resulted in limited outdoor movement and caused an overall decrease in patients attending both hospitals (Rainbow children's hospitals and LVPEI), thereby causing an impact on the recruitment of children in the study.

Another important component of the study was to do a retest of the visual functions, within a duration of 2 weeks. However, this was also impacted due to the second (partial) lockdown. Parents had concerns about reporting back to the clinic within a short duration and therefore in some children the retest was carried out beyond a 2-week duration (n=18) and therefore the study protocol was modified to include children within a 1 month retest period. . In addition to the retest of visual functions, comprehensive eye evaluations could not be carried out for all children due to these reasons.

Due to inadequate sample size for few parameters, it was difficult to draw conclusions of how these parameters affected visual functions. However, we did have quite a bit of data and were able to get some very valuable findings despite a small sample in certain areas.

3. **Summary of actions or decisions taken to mitigate for the impact of data collection or research activity that was prevented by COVID-19**

   All tests could not be performed on all the children with CVI, primarily due to the consequences of the pandemic. Although attempts were made to interpret all the study findings appropriately, for few parameters we have acknowledged an inadequate sample size as a study limitation due to which conclusive results could not be drawn in a small minority of areas.

4. **Summary of how any planned work might have changed the thesis narrative, including new research questions that have arisen from adjusting the scope of the research project**

   The repeatability indices of children with CVI were noted to be wider when compared to age-similar typically developing normally sighted children. However, this could only be reported in a small sample of children. As children with CVI can have wide ranging of functioning from low to high, it would be ideal to study the repeatability indices based on their visual functioning with an adequate sample size in each group.

Date of statement: 13 May 2023

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There have been a few individuals who have directly contributed to my study during the data collection phase. My heartfelt thanks to my former colleague and confidante **Premalatha Errolla** who has helped me with the functional vision assessment of children in this study. I also thank her for helping me with the video recordings and during my visual functions assessment procedure. I thank **Dr. Somashekhar Naraganti** and **Usha Hyndavi** for their help with the developmental assessment of children and for accommodating these assessments in their already busy clinics. I also thank them for patiently clearing all my doubts. I am grateful to **Jahnavi Kanchustambham** who politely agreed to view and analyse the videos for the current study. I also thank my colleagues at Special Needs Vision Clinic, Hyderabad campus, **Krishnapriya Kodavati**, **Jahnavi Kanchustambham** and **Navaneetha Ampolu** for their valuable insights in relation to my study. I profusely thank **Krishnapriya Kodavati** particularly for providing me clinical coverages whenever needed during my writing phase. My special thanks to my colleague and good friend **Vinay Kumar Tangellapalli** for his immense help with all the technical aspects in relation to the current study, particularly with the videos and photos. This helped me in several conference presentations I made during my PhD journey. I also thank him for all the support extended in helping me make the winning video of my PhD work for the Global Young Scientists Summit-2022.

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I would like to conclude the acknowledgement section here by most importantly thanking my **Lord and Saviour, Jesus Christ** for helping me come thus far. Truly, His grace has always been sufficient for me (2 Corinthians 12:9), particularly through this journey.

I am tempted to borrow the Rainbow children's hospitals tagline, *"It takes a lot to treat the little."* Indeed, it does! I am sure this long list in my acknowledgement section is a testament to that.

Disclosures

Conflicts of interest

Principal investigator/student: None

Supervisors: Dr. PremNandhini Satgunam has patent on an apparatus and a method to quantify visual patterns in infants. US Patent No.: US 10,517,475 B2. Indian Patent No.: 425672. This method and apparatus have not been used in this study.

Clinical collaborators: Dr. Stephanie Campbell is the Founder and Chief Executive Officer of OKKO Health, United Kingdom. The team donated an iPad with the OKKO Health application for testing its feasibility in the study cohort.

Contributors: None

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Abbreviations

CVI	Cerebral visual impairment
SEN	Special educational needs
HIE	Hypoxic Ischemic Encephalopathy
NHBI	Neonatal Hypoglycaemic Brain Injury
PVL	Periventricular Leucomalacia
DS	Down syndrome
VA	Visual acuity
CS	Contrast sensitivity
TAC-II	Teller acuity cards-II
PV	Peekaboo Vision
OCC	Ohio contrast cards
HH	Hiding Heidi
MAR	Minimum angle of resolution
LoA	Limits of agreement
CR	Coefficient of repeatability
MRI	Magnetic resonance imaging
DQ	Developmental quotient
DA	Developmental age
CA	Chronological age
EEG	Electroencephalography
ERG	Electroretinography
VEP	Visual evoked potential
OCT	Optical coherence tomography
SD	Standard deviation
GA	Grating acuity
CPD	Cycles per degree
CPCM	Cycles per centimetre
PVI	Perceptual visual impairment

Abstract

Background and Purpose

Several tests of visual functions have been developed and validated for typically developing children but very few have been validated in children with special educational needs (SEN). Cerebral visual impairment (CVI) which is a rising cause of paediatric vision impairment globally is a neurological condition categorized under the umbrella of SEN. Children with CVI are likely to have additional developmental delays in areas such as motor, speech, communication and cognition which makes assessment of visual functions challenging. In addition, other factors may also contribute to the variability of visual functions including location/extent of brain damage, overall development, seizures and medications used by these children. Measuring visual functions is therefore important in this population to understand how well a child performs visually and to understand the benefits of visual rehabilitation. Equally important is availability of visual function tools that are repeatable and can easily be carried out on this population. Children with CVI can present anywhere across low to high visual functioning and therefore validating the clinical tools to measure their visual functions is useful. The current study focused on validating clinical tools for the most commonly measured visual function, i.e., visual acuity (VA) and the parameter that relates closely with functional vision, i.e., contrast sensitivity (CS) in children with CVI by comparing the limits of agreement (LoA) between different tests of VA and CS and determining their repeatability indices. The association of visual functions with other factors such as: brain imaging findings, developmental quotient/age, seizure history/activity and functional vision score were also studied.

Methodology

Children aged 6 months to 7 years with a confirmed diagnosis of CVI by a paediatric neurologist were recruited primarily from a paediatric neurology clinic and some from a vision rehabilitation unit. Demographic and clinical information were elicited from the parents/caregivers and/or extracted from the medical records. Visual acuity was assessed using Teller acuity cards-II (TAC-II) and Peekaboo Vision application (PV app) and CS was assessed using the Hiding Heidi low contrast face test (HH cards) and Ohio contrast cards (OCC). Seizure history as reported by the parents/caregivers and the activity using the electroencephalography findings was noted. Developmental quotient was assessed using the Denver Developmental Screening Test-II (DDST-II) by a clinical psychologist. The brain imaging findings were scored by the neuro-radiologist based on the magnetic resonance imaging

(MRI) scanned films and the children were classified as having mild, moderate, and severe damage. The functional vision assessment was measured using the CVI range instrument and the children were categorized into phase I, II and III indicating low, moderate and high functioning CVI respectively. Intra-observer repeatability was carried out within a test-retest duration of 1 month. Chronologically age-similar typically developing children were recruited as the control group.

Results

Demographic and clinical characteristics of children with CVI

A total of 111 children with CVI with a mean age of 3.00±1.85 years (7 months to 7 years, 70.2% males) were recruited in the study. Neonatal hypoglycaemic brain injury was noted to be the most common aetiology of CVI (47.6%). The brain imaging findings revealed that a majority of the children were categorised as having severe damage (66.6%). The most common parent-reported visual concerns included difficulty in recognizing faces (45.4%) and maintaining eye contact (34.5%) in children ≤3 years. While maintaining eye contact (25%) remained as a concern for older children >3 years followed by missing objects in the lower/side field (17.5%).

Visual functions in children with CVI

The testability rates were found to be highest for TAC-II (95.4%) and HH cards (91.8%) in the VA and CS tests respectively. The testing times were noted to be comparable between the VA tests: TAC-II and PV app ($p=0.80$) and in CS, HH cards was found to be faster compared to OCC ($p<0.01$). The mean difference between PV app and TAC-II was -0.25±0.40 logMAR, 95% LoA was -1.03 to 0.53 logMAR and this was noted to be significantly different ($p<0.01$). The PV app over-estimated VA when compared to TAC-II by 0.25 logMAR. The mean difference between HH cards and OCC was 0.06±0.22 logCS, 95% LoA was -0.37 to 0.49 logCS and this was noted to be significantly different ($p<0.01$). The OCC cards under-estimated CS when compared to HH by 0.06 logCS. The intra-observer repeatability of tests carried out in 21 children with CVI revealed that TAC-II had better repeatability (coefficient of repeatability, CR=0.47) compared to PV app (CR=0.99). In CS tests, OCC had better repeatability (CR=0.24) when compared to HH cards (CR=0.55).

Relationship of visual functions with associative factors in children with CVI

The relationship between visual functions (i.e., VA and CS) and associative factors (such as: seizure frequency, developmental age, functional vision) was analyzed. Children having a seizure episode within the last 3 months had significantly poorer VA and CS measured using TAC-II ($p=0.03$) and OCC ($p=0.02$) respectively when compared to the children who had their last seizure episode greater

than 3 months ago. The VA, CS and developmental ages were significantly different across the 3 phases of CVI when the chronological age was adjusted, indicating that children with poorer VA, CS and developmental age belonged to low visual functioning group of CVI that was determined based on the functional vision score. Functional vision score was marginally strongly correlated with CS ($r=0.86$, $r^2=0.73$, $p<0.001$) when compared to VA ($r=-0.83$, $r^2= 0.68$, $p<0.001$). Functional vision score was also noted to have strong correlation with developmental age ($r=0.71$, $r^2=0.41$, $p<0.001$). Whereas, developmental age and visual functions were noted to have moderate correlation, i.e., VA: $r=-0.54$, $r^2=0.43$, $p<0.001$ and CS: $r=0.59$, $r^2=0.66$, $p<0.001$.

Controls

A total of 50 typically developing children were recruited as controls with a mean age of 3.39±1.87 years (6 months to 6.83 years, 38% males). The testability rates were found to be 100% for all the tests (TAC-II, PV app, HH cards and OCC). The testing times were noted to be shorter with the PV app when compared to TAC-II ($p=0.04$) and in CS, HH cards was found to have shorter testing time when compared to OCC ($p<0.01$). The mean difference between TAC-II and PV app was -0.14±0.30 logMAR, 95% LoA was -0.72 to 0.44 logMAR and this was noted to be significantly different ($p<0.01$). The PV app over-estimated VA when compared to TAC-II by 0.14 logMAR. The mean difference between HH cards and OCC was 0.27±0.11 logCS, 95% LoA was 0.06 to 0.49 logCS and this was found to be significantly different ($p<0.01$). Ohio contrast cards under-estimated CS when compared to HH by 0.27 logCS. The intra-observer repeatability of tests carried out in 16 children revealed that TAC-II had better repeatability (CR=0.27) compared to PV app (CR=0.41). In CS tests, OCC had better repeatability (CR=0.08) when compared to HH cards (CR=0.27).

Discussion and conclusions: The VA and CS estimates using the clinical tools were noted to be significantly different in both children with CVI and controls and the LoA was found to be narrower for the controls when compared to children with CVI. The PV app over-estimated VA when compared to TAC-II and OCC under-estimated CS when compared to HH cards in both groups. In addition to the vision impairment and delayed overall development in children with CVI, the different nature of the tests and step size of the values being measured (i.e., VA and CS) could be the main reasons for the difference in the values between the tests of visual functions. The intra-observer repeatability indices revealed that TAC-II had better repeatability when compared to the PV app. Therefore, indicating that it is not suggestible to use the tests of VA interchangeably. Ohio contrast cards was noted to have better repeatability indices when compared to HH cards and thereby also suggesting not to use the tests of CS interchangeably. This is important in order to avoid incorrect interpretation of the VA and CS

values particularly, when used as an outcome measure. It is also important to interpret the change in the VA and CS based on the test being used as each of them have different repeatability indices. In the current study, there was about 2 cards repeatability difference with TAC-II (VA test) and within 1 card repeatability difference with OCC (CS test). In addition, there was a strong correlation between CS and functional vision score. These findings indicate that CS is an essential parameter to be captured in children with CVI to understand their visual concerns better and for planning rehabilitative strategies. Developmental age and parent-reported visual concerns can serve as a referral parameter for paediatricians, paediatric neurologists and developmental psychologists. The visual functions and functional vision are likely to be influenced by the seizures and the overall development of the child and hence it is important to account for these parameters for planning medical interventions and rehabilitative strategies.

Chapter 1 : Background Information

1.1 Chapter overview

The first chapter will focus on the definitions and terminologies used commonly as part of describing special educational needs (SEN). The prevalence of SEN and cerebral visual impairment (CVI) for both developing and developed countries are also covered as part of this chapter. The following sections will include a detailed discussion about the different aspects of CVI including aetiologies, vision and developmental disorders and the final section will include the diagnostic/assessment tools used for children with CVI and the current management strategies.

1.2 Definitions and terminologies

The International Classification of Functioning, Disability and Health: Children and Youth Version (ICF-CY) states that disability is not merely limited to biological or social factors but rather is the interaction between health conditions, environmental and personal factors (World Health Organization., 2007).

According to the ICF-CY, disability with relation to vision could occur at three different levels:

a. an impairment in body function or structure, such as a cataract which prevents the passage of light and sensing of form, shape, and size of visual stimuli

b. a limitation in activity, such as the inability to read or move around

c. a restriction in participation, such as exclusion from school.

An example of a child with CVI, using ICF-CY classification is given in figure 1.1.

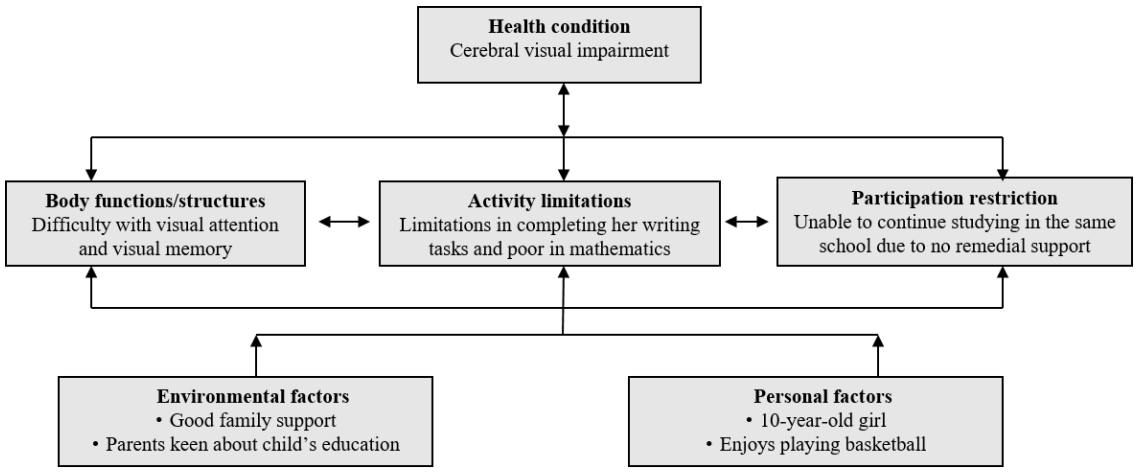

Figure 1.1: ICF-CY framework classification with an example of a child with CVI

"Persons with disabilities include those who have long-term physical, mental, intellectual or sensory impairments which in interaction with various barriers may hinder their full and effective participation

in society on an equal basis with others" (Convention on the Rights of Persons with Disabilities, 2006). With regards to children with disabilities, some may be born with a disabling health condition or impairment, whereas others may experience disability as a result of illness, birth trauma, genetic disorder or poor nutrition (e.g., children with cerebral palsy, Down syndrome (DS)) (World Health Organization & United Nations Children's Fund, 2012). These conditions may present with multiple disabilities, for example, a child with DS, can have flat feet and speech impairment as well.

The term 'special educational needs' (SEN) refers to a heterogeneous group of conditions that result in developmental delays that could involve isolated or multiple sensory and motor functions (Mauro, 2018). Guidelines for clinical diagnosis of various conditions listed under special needs is described in the Diagnostic and Statistical Manual of Mental Disorders, in the International Classification of Diseases (ICD)-9th edition (Special needs (In Wikipedia), revised in 2023) and in the recent ICD-11 (ICD-11 for Mortality and Morbidity Statistics, (version: 01/2023)). Special educational needs is non-uniformly defined across various regions in the world. In India, the term disability is more commonly used in place of SEN. The Cambridge English dictionary (Essential British English version) defines special needs as 'the particular things needed by or provided to help people who have an illness or condition that makes it difficult for them to do the things that other people do', whereas disability is defined as 'an illness, injury or condition that makes it difficult for someone to do the things that other people do'(Cambridge University Press and Assessment, 2023). 'Person with disability' means a person with long term physical, mental, intellectual or sensory impairment which, in interaction with barriers, hinders his/her full and effective participation in society equally with others (The Rights of Persons with Disabilities Act, 2016). 'Multiple disabilities' refers to a combination of two or more disabilities of the person with disabilities (Persons with Disabilities (section 2), 1995). The terminology, however, is viewed differently in developed countries such as the United Kingdom (UK). The term SEN is interchangeably used for special needs, wherein the focus is more on the educational context of children with special needs (SEND code of practice:0 to 25 years., 2014). Irrespective of the varying perspective of SEN, the challenges that these individuals face remain the same that include either one or more impairments in the areas of motor, speech, cognition, hearing and vision. The most common conditions are cerebral palsy, DS, autism spectrum disorder, CVI, delayed visual maturation, behavioural disorders (for example attention deficit hyperactive disorder), learning disabilities and conditions arising due to prematurity (Blanco & Chapel, 2018). Cerebral visual impairment is one of the most common neurological conditions resulting in visual and perceptual impairments due to dysfunction of retrochiasmatic visual pathways and cerebral structures (Lueck & Dutton, 2015; Pehere

et al., 2019). It is defined as *"a verifiable visual dysfunction which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment"* (Pilling et al., 2022).

1.3 Prevalence of children with special educational needs

Global estimates

According to the most recent 2010 global estimates by the World Health Organization, approximately 16% of the world's population has some form of disability (~1.3 billion) (World Health Organization & World Bank., 2011). The Global burden of disease study estimates that, 95 million children (5.1%) between the ages of 0-14 years are blind and 13 million (0.7%) of these children have severe disability (World Health Organization & World Bank., 2011).

India

Approximately 80% of the world's disabled population are from developing countries (Disability Inclusive Development in UNDP, 2018). In India, approximately 2.21% of the total population are disabled according to the 2011 census. Amongst this population, 20% are disabled due to motor disability, 19% due to vision and hearing impairment and 8% have multiple disabilities, i.e. 2 or more disabilities (Disabled persons in India: A statistical profile., 2016) (figure 1.2).

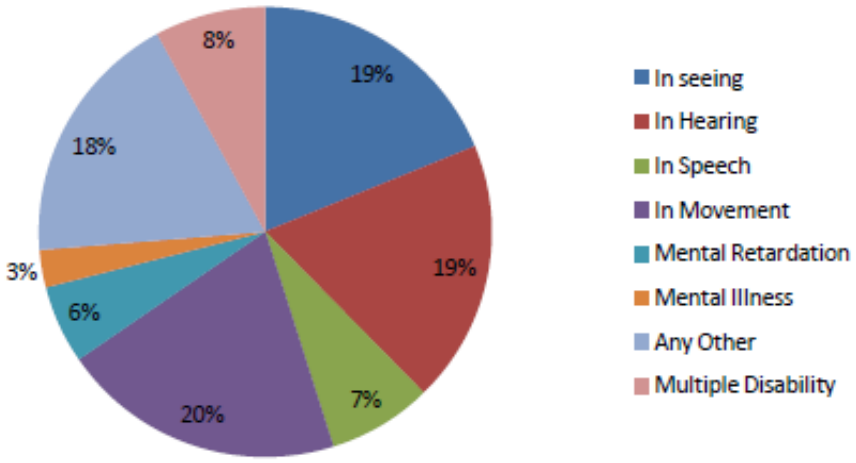

Figure 1.2: Pie-chart illustrating various disabilities amongst the disabled population in India
(Extracted from Disabled Persons in India: A Statistical Profile 2016)

In India, childhood disability accounts for a total of 1.24% (2.042 million) among children aged 6 years and under, of whom 30% have vision impairment and 7% of the children have multiple disabilities (Disabled persons in India: A statistical profile., 2016)) (figure 1.3).

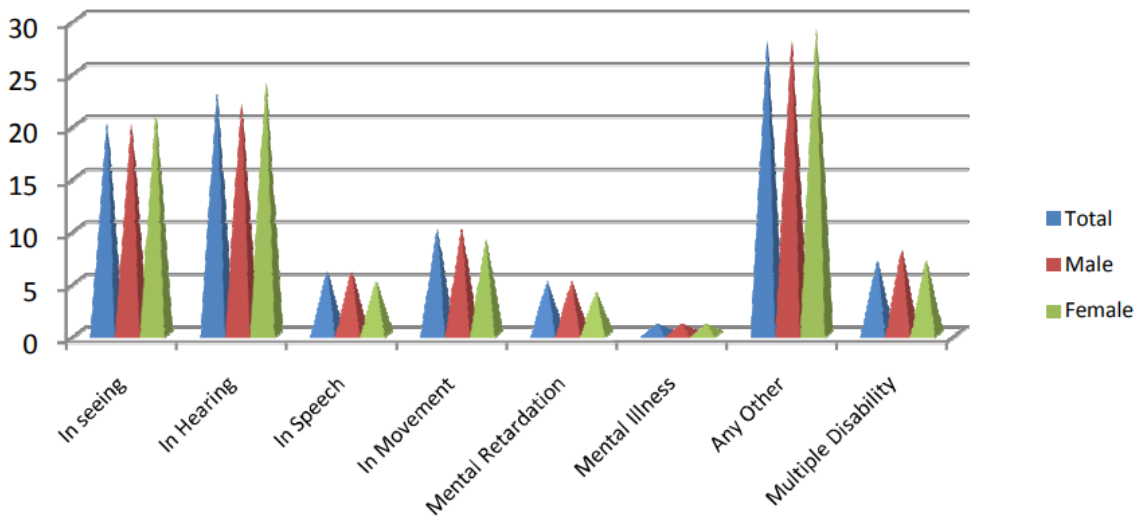

Figure 1.3: Cone (column) chart illustrating various disabilities among children (0-6 years) in India

(Extracted from: Disabled Persons in India: A Statistical Profile 2016)

United Kingdom

In the UK, 22% (14.6 million) of the total population self-reported a disability and approximately around 9% of children in the UK were recorded as having a disability during the year 2020-21. This is based on the family resources survey which also highlights that the proportion of population reporting a disability has increased by upto 4% points when compared to 2010-2011 (Kirk-Wade, 2022). According to figures from the Royal National Institute of Blind People (RNIB), UK in 2022, a total of 25,000 children aged 0 to 16 years had vision impairment in the UK and about 15,000 between the ages of 17-25 years. About 50% of these children and young adults were also noted to have SEN ("Education and children, young people and families research," 2022).

The fact that children with SEN have visual concerns that often go unnoticed and unreported has been well documented in several studies (Das et al., 2010; Gothwal et al., 2017; Welinder & Baggesen, 2012; Woodhouse et al., 2014). The undetected visual abnormalities can go a long way in having an adverse effect on the child's overall development (Reynell, 1978; Sonksen et al., 1991). The most common ocular abnormalities observed in this cohort included uncorrected refractive errors, strabismus, lenticular abnormalities, retinal and optic nerve pathologies and cortical level abnormalities (Gothwal et al., 2017). Salt and Sargent had discussed key studies outlining the vision impairment, refractive errors and strabismus in children with SEN that include conditions such as preterm birth abnormalities, cerebral palsy, visual conditions arising due to ocular or

neurological/neuro-developmental conditions (such as CVI, learning disability, DS and severe hearing impairment (Salt & Sargent, 2014) (table 1.1).

Clinical parameters	**Intellectual disability (IQ<80) (Nielsen et al., 2007; Welinder & Baggesen, 2012) %**	**Intellectual disability (IQ<50) (Nielsen et al., 2007; Welinder & Baggesen, 2012) %**	**DS (school age) (Creavin & Brown, 2009) %**	**CP (Surman et al., 2006), (Woo et al., 2011) %**	**Preterm birth (O'Connor et al., 2004), (Holmstrom et al., 2014) %**	**General population (Rahi et al., 2003) (Sandfeld Nielsen et al., 2007) (Donnelly et al., 2005) %**
Visual acuity (VA) ≤6/60	3.8	22.4	-	-	1-3 (O'Connor et al., 2004)	-
VA<6/60	-	-	-	9-11 (Surman et al., 2006) 5 (Woo et al., 2011)	0.8 (Holmstrom et al., 2014)	0.06 (Rahi et al., 2003)
VA≤6/18	10.5	9	-	-	2.5 (O'Connor et al., 2004) (≤6/24)	0.16 (Sandfeld Nielsen et al., 2007)
VA<6/18	-	-	-	-	-	0.13 (Donnelly et al., 2005)
All refractive errors (hyperopia≥+ 2D)	44	-	55	60 (Woo et al., 2011)	19 (O'Connor et al., 2004) (<35 weeks)	4.5 (Sandfeld Nielsen et al., 2007)
Myopia	11 (<-0.5)	16 (<-0.5)	13 (<-0.75)	46.6 (Woo et al., 2011) (≤1.5)	10-18.9 (O'Connor et al., 2004)(<0)	1.39 (Donnelly et al., 2005) (≤0.75)
Hyperopia (≥+2.0D)	24	-	-	10.2 (Woo et al., 2011) (≥+1.5)	-	0.13 (Donnelly et al., 2005)
Hyperopia (≥+3.0D)	15.3	21.8	42	-	4-6.6 (O'Connor et al., 2004)	0.9 (Sandfeld Nielsen et al., 2007)
Astigmatism (<-1.0cyl D)	20.6	34.7	37.5	20.5 (Woo et al., 2011) (≥3.0)	13.7 (O'Connor et al., 2004)	4.1-7.7 (Sandfeld Nielsen et al., 2007) (≥1.0) D
Strabismus	27	-	25	59 (Woo et al., 2011)	13.5-44 (Holmstrom et al., 2014; O'Connor et al., 2004)	4-7.5 (Donnelly et al., 2005; Sandfeld Nielsen et al., 2007)

Table 1.1: Key studies comparing vision impairment and refractive errors in children with special educational needs

(Extracted from: Salt A and Sargent J, Arch Dis Child, 2014)

(IQ: Intelligence quotient, D: Dioptres, DS: Down syndrome, CP: Cerebral palsy)

1.4 Cerebral visual impairment

Cerebral visual impairment is an encompassing term that gives rise to various visual and perceptual impairments due to the dysfunction of the visual pathways beyond the lateral geniculate body (Lueck & Dutton, 2015). The terms cortical and cerebral are often used interchangeably when referring to CVI by clinicians and researchers, however, it is best to refrain from doing this as both terms vary based on the severity and the location of the damage. Cortical visual impairment refers to damage occurring in the neuro-cortex without any damage to the sub-cortical areas such as the basal ganglia, thalamus, hypothalamus etc. Cerebral visual impairment on the other hand refers to the involvement of both the cortical and sub-cortical regions (Merabet et al., 2017).

With advancements in medical care, there is a significant improvement in neonatal and intensive care units. This in turn reflects on the increasing survival rate of children with cerebral pathology over the years (Rudanko et al., 2003), which is also observed in developing countries such as India (Pehere et al., 2018).

1.4.1 Prevalence of CVI

Cerebral visual impairment was reported as the most common cause of profound vision impairment in a retrospective study of 428 children with severe vision impairment ≤3 years of age visiting a tertiary eye care unit located in southern India. (Pehere et al., 2019). In developed countries such as England and Wales, CVI has emerged as the commonest single cause of severe vision impairment in children and accounted for 21%-31% of certifications for visually impaired, out of a total of 1040 certifications in 2009-10 (Mitry et al., 2013). As per the national registry of children record of the United States, CVI was noted to be the most common cause of vision impairment in children enrolled for specialized early intervention programs (Hatton et al., 2007). In children with developmental delays such as cerebral palsy, DS or in risk-factors such as prematurity, hypoxic ischemic encephalopathy (HIE), hydrocephalus and meningitis, CVI was noted to affect approximately 20-90% of children (Black et al., 2019; Chokron et al., 2020; Dutton et al., 2004; Ho et al., 2020; Woodhouse, 1998). Findings of a large school vision screening cohort (5-11 years) revealed that on an average of 1 in every class of 30 children had atleast one CVI-related vision problem (Williams et al., 2021).

1.4.2 Aetiology

Hypoxic ischemic encephalopathy (Pehere et al., 2018), neonatal hypoglycaemic brain injury (NHBI) (Tam et al., 2008) and periventricular leucomalacia (PVL) (Jasper & Philip, 2018) are the most commonly reported causes of CVI. The other causes include metabolic disorders, genetic causes, brain

infections, brain malformations, epilepsy, hydrocephalus, focal brain lesions etc (Bosch et al., 2014). The most common causes are discussed in detail below.

Hypoxic Ischemic Encephalopathy

Hypoxic ischemic encephalopathy is one of the most common aetiologies of CVI. The condition can occur in both full-term and pre-term babies and the extent of severity of the brain damage could be different as well (Johnston et al., 2002). The most common risk factors for HIE include older maternal age, gestational diabetes, pre-eclampsia, placental abruption, cord prolapse, uterine rupture, shoulder dystocia, lower socioeconomic status, mode of delivery or meconium aspiration syndrome (Badawi et al., 1998; Hayes et al., 2013; Kurinczuk et al., 2010).

The pathophysiology of HIE

As the name suggests, lack of oxygen and blood supply to the brain results in HIE. This disruption of blood and oxygen, causes an initial increase in the blood pressure and cerebral blood flow. The redistribution of blood is favoured to the vital parts such as the brain, heart and adrenal glands. There are various consequences due to this disruption. The initial phase of the HIE is called the primary energy failure wherein there is a drop in the adenosine triphosphate (ATP) hydrolysis because of a decrease in glucose levels. This causes an increase in the intracellular calcium and extracellular glutamate (excitatory neurotransmitter) resulting in excitotoxicity and necrosis. Following this there is a latent phase of HIE which lasts approximately 30 minutes, in which there is normalization of homeostasis. The efforts here are directed to continue to keep lowered body temperature, i.e., approximately 91F. This is achieved through hypothermia therapy that is achieved by placing the child on a cooling mat or by putting on a cooling cap. By reducing the body temperature, the energy demand reduces which can avoid further damage to the cells. If hypothermia therapy is not carried out during the latent phase, the new-born is likely to enter into the secondary energy failure phase which is more profound as it can affect the mitochondrial function of the cells and can potentially cause apoptosis. The final phase of HIE is the tertiary energy failure phase which can occur within days after the brain injury and can continue for months. This phase includes late cell death, remodelling and repair (Rocha-Ferreira & Hristova, 2016) (figure 1.4).

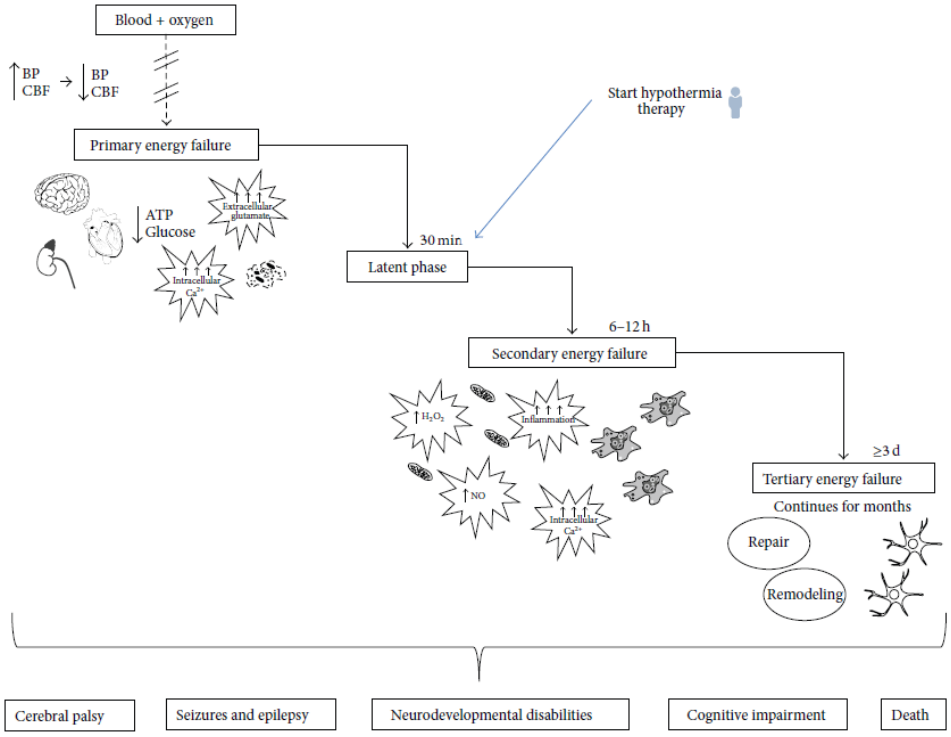

Figure 1.4: Schematic representation of the different phases of hypoxic ischemic encephalopathy

(Extracted from: Rocha-Ferreira E and Hristova M, 2016)

Neontal hypoglycaemic brain injury

The critical threshold value of blood glucose levels <47 mg/dl has been noted to have neurodevelopmental outcomes (Lucas et al., 1988). Gestational diabetes in insulin-dependent women during pregnancy is one of the most common risk factors for the occurrence of neonatal hypoglycaemia. The presence of high glucose in the intrauterine environment results in a relative increase in fetal insulin secretion (Güemes & Hussain, 2015). These insulin levels, continue to remain high due to inhibition of metabolic compensation mechanisms (hyperinsulinemia) in the neonate. This can significantly drop glucose levels in the neonate and results in NHBI, the effects of which are usually irreversible to the areas of the brain (Voormolen et al., 2018). Regular blood glucose screening of neonates of mothers having gestational diabetes has been recommended in the first 12 hours of life (Voormolen et al., 2018). The other causes include delay in breastfeeding the neonate primarily due to poor guidance to the mother as part of antenatal counseling (DiGirolamo et al., 2003). As per the guidelines by the Academy of Breastfeeding, the first feed to the all term neonates should be initiated within the first 30-60 minutes of life and should be as frequent as 10-12 times per 24 hours for the first few days of life (Wight et al., 2014).

Periventricular leucomalacia

Several imaging studies help us understand the areas of the brain that are predominantly affected in a full-term vs. a pre-term neonate. The cerebral cortex, brain stem and selective parts of the sub-cortical region such as the thalamus and basal ganglia are noted to be commonly affected in the full-term neonate (Johnston et al., 2001; Martin et al., 1997). Whereas, because of the poorly developed areas as observed in the immature brain of the pre-term neonate (especially in gestational age <32 weeks), the severity may differ (Johnston et al., 2002). The watershed areas of the brain, supplied by the major cerebral arteries are the most vulnerable in case of a hypoxic ischemic event. This disrupts the blood supply to the other parts of the brain and soon affects the oligodendrocytes at the periventricular region, which eventually causes white matter damage (Ahya & Suryawanshi, 2018), therefore called periventricular leucomalacia (PVL). This terminology has been recently revised to white matter damage of the brain as the damage may not just be limited to the periventricular region alone (Thekkeveedu, 2020).

1.4.3 Vision disorders in children with CVI

As CVI is a complex visual cognitive-perceptual dysfunction with broader variations in clinical characteristics, it is not easy to specifically diagnose the condition as it often gets labelled as delayed visual maturation and retinal or optic nerve disorders (Jasper & Philip, 2018). Common ocular abnormalities associated with CVI include refractive errors (Matsuba & Jan, 2006; Ozturk et al., 2016), an impaired emmetropization process (Saunders et al., 2010), accommodative anomalies (particularly hypoaccommodation) (Saunders et al., 2008) and eye movement disorders such as strabismus and nystagmus (for e.g. deficient smooth pursuits and incomplete saccades) (Fazzi et al., 2007). Cataract, coloboma, retinal dystrophies and optic nerve anomalies have also been noted in this cohort (Fazzi et al., 2007; Jacobson et al., 1998). Retinopathy of prematurity has been observed to be associated with PVL (Jacobson et al., 1998). A retrospective review of medical records carried out in Indian children with CVI revealed that approximately 50% had significant refractive errors, 49% had strabismus, 12% had hypoaccommodation and approximately 4% had cataract. (Pehere et al., 2018). The various reasons for a lack of comprehensive examination include the lack of resources (human, clinical equipment and infrastructure), lack of training among eye care professionals to assess and manage children with neurological conditions, lack of awareness among eye care professionals and caregivers about the potential benefits of having a comprehensive eye examination in children with brain damage and as the examination process may be time consuming (Pehere et al., 2018). Often the parents'/caregiver's emphasis is more on the obvious disabilities that may co-exist in these children

such as inability to walk (motor), inability to talk (speech) and comprehend instructions (cognitive) and the visual needs remain unmet. Most of the treatable eye conditions in CVI remain undiagnosed.

1.4.4 Higher-order visual processing in children with CVI

The severity of the vision impairment can vary from severe/profound to near-normal/normal acuity, but with abnormalities in the higher order visual processing (which is also referred to as high functioning CVI) (Pehere & Jacob, 2019). The dorsal and ventral streams arising from the occipital lobe can be affected due to CVI and thereby cause difficulties in visual processing. (figure 1.5) The dorsal stream also referred to as the 'where pathway' (a sub-cortical function (Atkinson, 1992)) initiates from the primary visual cortex in the occipital lobe and travels towards the parietal lobe. Dysfunction in this pathway can potentially result in impaired visual guidance of body movements, visual inattention, neglect, gaze apraxia and simultanagnosia. On the other hand, the ventral stream also referred to as 'what pathway' (a cortical function (Atkinson, 1992)) arises from the occipital lobe and travels towards the temporal lobe. Dysfunction in this pathway can potentially result in impaired face and object recognition, poor visual memory and difficulty in orienting in familiar environments (Jasper & Philip, 2018) (table 1.2). Both the dorsal and ventral stream together enable our seamless perception of the visual information and the interactions between both pathways has also been well established (Cloutman, 2013).

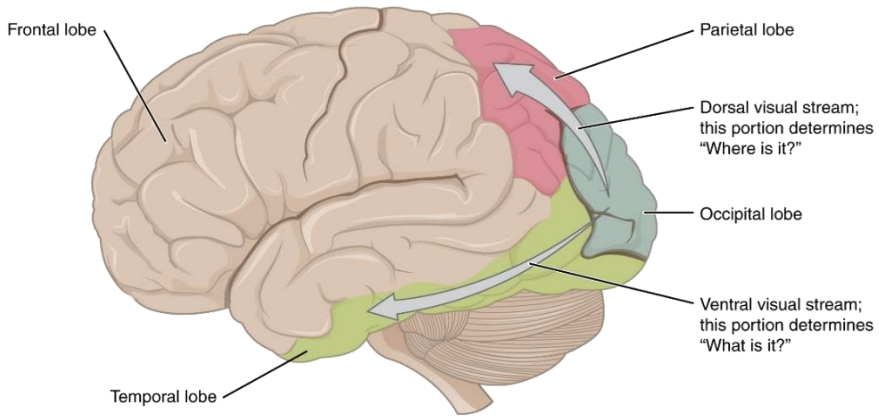

Figure 1.5: The dorsal and ventral pathways

Image source: Anatomy & Physiology, Connexions website

(Creative commons license link: https://commons.wikimediaorg/wiki/File:1424_Visualsfsf_Streams.jpg#file)

Characteristics of dorsal stream visual dysfunction
Impaired:
1. Ability to handle complex scenes in two-dimensional and three-dimensional space
2. visual search
3. Visually guided movement of upper and lower limbs
4. Visual attention Impaired perception of motion
Characteristics of ventral stream visual dysfunction
Impaired:
1. Recognition of faces, objects, shapes, letters, or gestalt
2. Visual memory
3. Orientation

Table 1.2: Primary characteristic features of dorsal and ventral stream dysfunction
(Modified and adapted from: Orbitus et al, 2011) (Ortibus et al., 2011b)

1.4.5 Developmental delays in children with CVI

Developmental delays are common in children with CVI. Around 60-70% of children with cerebral palsy are noted to have CVI (Schenk-Rootlieb et al., 1992) and therefore developmental delays in motor, speech and cognition are more pronounced in this cohort (Pehere et al., 2018), including hearing loss in a smaller minority (Khetpal & Donahue, 2007). Among children with gross motor delays, probable[1] or definite[2] CVI was present in almost all children with spastic quadriplegia (100%) and spastic diplegia (99%). Only probable CVI was noted in a small minority of children with spastic hemiplegia (10.8%) and none among non-spastic cerebral palsy (Jasper & Philip, 2018). Poor academic performance has also been linked to CVI (Molloy et al., 2017).

1.4.6 Visual concerns in children with CVI

Delays in speech and cognition restrict children with SEN from communicating their visual concerns. Therefore, clinicians invariably rely on parents or other primary caregivers for understanding the visual concerns in these children. The importance of a structured history taking has been highlighted in order to obtain all the relevant history to plan appropriate assessment and management for children with CVI (Lueck et al., 2019) (Philip & Dutton, 2014).

[1]Diagnosed in children <1 year of age based on the history suggestive of CVI, but when the clinical examination is inconclusive
[2] Diagnosed in children based on both history and clinical examination suggestive of CVI

Some of the concerns that should be captured as part of the history taking include: having difficulty in face recognition, maintaining eye contact, understanding facial expressions, following fast gestures, difficulty working in cluttered environments, ignoring specific sides, difficulty recognizing objects, shapes and letters, difficulty remembering routes and difficulty reaching out to objects when presented (Lueck et al., 2019). The PI carried out a preliminary study by auditing the records of children with SEN attending a specialist clinic (Special Needs Vision Clinic) at L V Prasad Eye Institute (LVPEI), Hyderabad, India. The visual concerns documented have been discussed in section 4.2 (preliminary study 1).

1.5 Diagnostic and assessments tools used in children with CVI

Cerebral visual impairment still remains the diagnosis of exclusion, i.e. it is diagnosed primarily when visual abnormalities cannot be attributed to the defects in the anterior visual pathway (McConnell et al., 2021). McConnell et al's systematic review includes a detailed description of the tests used to diagnose and assess children with CVI. They are classified broadly as follows: (1) Medical history, (2) Vision assessment/ophthalmologic examination, (3) Neuroimaging, (4) Visual behaviour and direct observation, (5) Structured history-taking, (6) Visual perception tests, (7) Ocular movement and posture assessment, (8) Intelligence/IQ assessment, (9) Clinical electrophysiology and (10) Neurodevelopmental tests (McConnell et al., 2021).

This section will discuss about the commonly used clinical tools and assessment methods that are used to diagnose CVI. Vision assessment tests used in children with CVI include tests of basic visual functions and also that of higher-order visual processing. Chapter 3 discusses the most commonly used VA and CS tools in children with SEN and in typically developing infants and young children. In addition to the diagnostic tests that are used to confirm CVI, this section will also cover the higher-order vision assessment tests *(often called as visual perceptual tests)* used in children with CVI, functional vision assessment and also the CVI-specific questionnaires that are useful in diagnosing CVI and to plan better rehabilitative strategies.

1.5.1 Medical history

The medical history forms the basis for suspecting CVI and for advising tests to diagnose the condition. More often than not the primary clinician who makes this diagnosis is a paediatric neurologist and, in a few cases, the paediatric ophthalmologist, once referred. Neonatal birth history is essential and should capture any hypoxic and hypoglycaemic event, which may have occurred. Other co-morbidities such as, hydrocephalus, central nervous system infections, traumatic injury to the brain

and any metabolic disorders and cerebral palsy should be enquired about (McConnell et al., 2021). It is also important to ask about a history of seizures. Other important history taking points include gestational age, type of delivery, maternal history and the child's developmental milestones.

1.5.2 Neuroimaging

Neuroimaging is very commonly carried out in order to establish the diagnosis of CVI and to understand the relationship between brain damage and vision impairment (Good et al., 2001; Mathur et al., 2010; Murakami et al., 2008). Previous studies have reported the use of cranial ultrasound and computed tomography (CT) as part of the assessment process in infants and young children (Eken et al., 1994; Ipata et al., 1992; Schenk-Rootlieb et al., 1994). However, recent studies have focused on the findings of magnetic resonance imaging (MRI) (Cioni et al., 2000; Sakki et al., 2021), as the latter offers better sensitivity to the structural changes in the brain (Merabet et al., 2017). Efforts are being made to explore the latest imaging techniques such as HARDI (Bauer et al., 2014) and diffusion tensor imaging (DTI) tractography (Kelly et al., 2021) for an in-depth understanding of the extent and location of the specific damage.

Grading systems (table 1.3) based on the extent and location of the brain damage have been used to understand the association between brain damage and developmental quotients and also with vision-related parameters such as: visual functions and functional vision (Cioni et al., 2000; Cioni et al., 1996). The different areas that are studied include: optic radiations, visual cortex, lateral ventricles, corpus callosum, white matter, presence of cysts, subarachnoid space etc (Kozeis, 2010; Philip & Dutton, 2014). Optic radiations (Cioni et al., 2000; Cioni et al., 1996), thinning of corpus callosum (Cziker et al., 2009) and white matter reduction (Lanzi et al., 1998) were most commonly associated with vision-related parameters.

Abnormality	Grading	Description
Size of lateral ventricles	Grade 1	Normal size of both ventricles
	Grade 2	Unilateral enlargement or bilateral mild enlargement
	Grade 3	Bilateral severe enlargement
WM abnormal signal intensity	Grade 1	Normal WM or only focal involvement of PV-WM
	Grade 2	Diffuse involvement of PV-WM in both hemispheres or involvement of SC-WM in one hemisphere
	Grade 3	Involvement of SC-WM in both hemispheres
WM reduction	Grade 1	Not reduced
	Grade 2	Reduction of PV-WM in both hemispheres or of deep WM diffusely in one hemisphere
	Grade 3	Reduction of deep WM diffusely in both hemispheres
Cysts	Grade 1	No cysts
	Grade 2	Small cysts (n<3) bilateral in PV regions or unilateral cystic lesion (small or large)
	Grade 3	Bilateral multiple cysts (small or large) involving PV regions and/or deep WM
Size of subarachnoid space	Grade 1	No enlargement
	Grade 2	Bilateral diffuse mild enlargement or severe enlargement only in one hemisphere
	Grade 3	Diffuse severe enlargement in both hemispheres
Corpus callosum	Grade 1	Normal or thinning involving the posterior body
	Grade 2	Thinning involving the total body
	Grade 3	Diffuse thinning
Cortical matter (ulegyria and cortical dysplasia)	Grade 1	No cortical abnormalities
	Grade 2	Unilateral cortical abnormalities
	Grade 3	Bilateral cortical abnormalities
Total score	Grade 1	Sum of previous scores: 7-11
	Grade 2	12-16
	Grade 3	17-21
Visual cortex	Grade 1	No impairment
	Grade 2	Moderate impairment
	Grade 3	Severe impairment
Optic radiations	Grade 1	No impairment
	Grade 2	Moderate impairment
	Grade 3	Severe impairment

Table 1.3: Revised grading of magnetic resonance imaging findings commonly noted in children with CVI

(Extracted from Cioni et al, 2000 (Cioni et al., 2000))

WM: white matter, PV: periventricular, SC: sub-cortical

1.5.3 Developmental assessment

Developmental quotient (DQ) is a global score that is assigned to a child based on his/her overall development in all milestones in comparison with age-appropriate norms (Accardo et al., 2008).

$$\text{Developmental quotient (DQ)} = \frac{\text{Developmental age (DA)}}{\text{Chronological age (CA)}} \times 100$$

The most commonly assessed parameters include the following: motor skills - gross and fine motor, speech and language development – expressive and receptive, social and emotional, cognition (Bedford et al., 2013) and in few tools the domain of visuomotor is added as well (Ounsted et al., 1983). There are several instruments that have been used in earlier studies for the assessment of the DQ by child psychologists and developmental paediatricians. The most popular instruments include the Griffiths mental developmental scale (Griffiths, 1954), Denver developmental screening test-II (DDST-II) (see appendix A13) (Glascoe et al., 1992) and Bayley scales of infant and toddler development (Bayley, 2006). There are a few other instruments that are used for screening the developmental milestones based on the responses given by the parents/caregivers, such as the Ages and stages questionnaire (Singh et al., 2017), Oregon skills inventory (Brown, 1978) and Parents' Evaluation of Developmental Status (Woolfenden et al., 2014).

A small number of studies have reported strong correlation between developmental scores and vision-related parameters in children with CVI (Cioni et al., 2000; Eken et al., 1995). Vision impairment was observed to be the most significant variable in predicting poor neuro-developmental scores compared to motor skills and the extent of lesions noted on brain imaging in children with periventricular leucomalacia (Cioni et al., 2000).

1.5.4 Clinical electrophysiology

a. Electroencephalography (EEG)

Seizures are one of the most commonly associated neurological deficits in children with CVI (Huo et al., 1999). The type and frequency of the seizures can vary based on the location of the brain damage.

The different types of seizures noted in children with CVI are discussed below:

1. Generalized seizure: These can arise due to damage being present on both sides of the brain.

a. Absence seizures (or petit mal seizures): These can often go unnoticed by the parents/caregivers. The most commonly noted signs include rapid blinking for few seconds and non-purposeful gaze.

b. Tonic-clonic seizures (or grand mal seizures): These types of seizures are obvious and are usually reported by the parents/caregivers. Children with tonic-clonic seizures could lose consciousness, cry out or make other loud noise, fall, or have muscle spasms/jerks (Types of Seizures., 2020).

2. Focal seizures (or partial seizures): These types of seizures arise due to damage to any one area of the brain.

a. Simple focal seizures: These seizures arise due to a small part of the brain being affected. These can cause a change in sensation, such as a strange taste or smell.

b. Complex focal seizures: These seizures could cause confusion to the person and inability to respond to any questions or direction for few minutes.

c. Secondary generalized seizures: These seizures can initiate in one part of the brain (focal seizure), but are likely to spread to both sides of the brain (generalized seizure) (Types of Seizures., 2020).

Electroencephalography is one of the most commonly used electrophysiological techniques used as part of a battery of tests carried out on children with CVI. This helps us understand the brain activity and the likelihood of seizure episode and if present, the specific type of seizure (McConnell et al., 2021). Through this electrophysiological procedure, the neurons that are activated produce current flows. This is quantified during the synaptic excitations of dendrites of several pyramidal neurons in the cerebral cortex. The difference of electrical potentials arises due to the cumulative post synaptic graded potentials from the pyramidal cells that generate electrical dipoles between the body of the neuron (soma) and the neural branches (apical dendrites). The electric activity of the human brain starts around 17-23 weeks of prenatal development and it is assumed that the total number of neural cells are already developed at birth (Nunez, 1995).

The various EEG findings commonly noted in children with CVI are discussed below: Infantile spasms are one of the commonly noted epileptic syndromes that rarely has onset in children older than 2 years. These seizures usually begin in children younger than 1 year of age and has features of epileptic spasms, with or without hypsarrhythmia (Caraballo et al., 2011). Hypsarrhythmia are the most common random or chaotic high-amplitude slow waves with intermixed multifocal spikes (Lux & Osborne, 2004). A longitudinal study on neurological abnormalities in children with CVI revealed that

78.6% of the children had epilepsy, among which 33.8% had epileptic encephalopathy with spasms/hypsarrhythmia being the most common (Jimenez-Gomez et al., 2022). A majority of the children with seizures (75.9%) were categorized as having poor seizure control (Jimenez-Gomez et al., 2022), which was defined as having more than one seizure per month over at least 6 months (Chawla et al., 2002).

b. Visual evoked potential (VEP)

Visual evoked potential is an electrodiagnostic procedure to assess the anterior visual pathway upto the optic chiasm. However, the outcome of the test depends on the integrity of the pathway all the way upto the cerebral cortex (Tripathy et al., May 2022). The signals are recorded through electrodes placed on the occipital region and elicited from light flashes or by patterned stimuli. Damage along the pathway is evident through the reduced signal. The VEP is essentially a function of central visual, as such a large region of the occipital cortex belongs to macular projections. Hence, peripheral visual loss may be overlooked. The two most commonly used techniques include the flash (suitable for children with severe vision impairment and in neonates), pattern (provides a more quantifiable and reliable waveform) (van Baar, 1998).

In children with severe vision impairment due to CVI, the flash VEPs were noted to be maximally localised to non-standard regions of the scalp (Handley & Liasis, 2017). Findings such as atypical morphology and also significantly decreased amplitude or increase in latency were observed (Kuba et al., 2008). Multifocal VEP (mfVEP) is a new technique that has been developed to detect small abnormalities in optic nerve transmission and to provide topographic correlation along the visual pathway. It allows recording simultaneously from multiple areas of the visual field (Klistorner et al., 1998).

Studies suggest that the acuity values obtained with VEP, and behavioural techniques (such as Teller acuity cards (TAC)) are significantly different in children with neurological vision impairment. The VEP technique yielded better acuity values (Good, 2001; Lim et al., 2005), with the exception of one study in children with the etiology of PVL (Tinelli et al., 2008). In a recent retrospective review carried out on children with CVI, it was noted that acuity estimates using VEP were equal to 1 or more octaves when compared to that obtained using preferential looking technique. This quantifiable disparity was suggested to be used as a biomarker of CVI (Raja et al., 2021). Attention to the card being presented was speculated to be the most possible cause for poorer acuity values with behavioural techniques (Orel-Bixler et al., 1989).

c. Electroretinography (ERG)

Electroretinography is a commonly used tool to study the functional integrity of the retina and particularly beneficial in preverbal children to arrive at the diagnosis early on (Parness-Yossifon & Mets, 2008). However, in children with CVI, ERG was not noted to directly contribute towards diagnosing the condition, but helpful in ruling out the retinal causes (Pilling et al., 2022; Whiting et al., 1985).

1.5.5 Optical Coherence Tomography (OCT)

Optical coherence tomography is a non-invasive procedure used for retinal and optic nerve imaging (Avery et al., 2015). Optic disc examination using the OCT is being used increasingly in children with CVI, particularly with PVL aetiology, as optic disc related cupping is more often noted in this cohort (Groth et al., 2020; Jacobson et al., 1997). Visual field defects are common in children with CVI and performing a conventional visual field assessment could be challenging in this group of children (Pilling et al., 2022). Therefore OCT is helpful in identifying the focal thinning of the ganglion cell layer that corresponds to the visual field defects (Jacobson et al., 2019).

1.5.6 Oculomotor assessment

Several oculomotor disorders are reported among children with CVI (Salati et al., 2002). These include fixation impairment such as instability, poor saccadic and smooth pursuits (Philip & Dutton, 2014; Salati et al., 2002), variable angle strabismus and nystagmus (Khetpal & Donahue, 2007). It is important to examine oculomotor deficits in detail to plan effective rehabilitative strategies (Salati et al., 2002).

1.5.7 Visual field assessment

Visual field defects in children with CVI could range from partially to severely constricted fields, depending on the location and extent of the brain damage (Jacobson et al., 2010). In children with CVI, the most commonly noted field loss in the bilateral inferior field due to the lesions affecting the upper optic radiations on both sides (Philip & Dutton, 2014). Another commonly noted visual field defect in this cohort is homonymous hemianopia due to damage to the postchiasmal visual pathways in one of the brain's hemispheres (Handley et al., 2022). The feasibility of performing standard automated perimetry (such as Humphrey visual fields) in children with CVI is limited (Merabet et al., 2016). Therefore, determining field loss through confrontation technique was noted to be more feasible (Bosch et al., 2014). Satgunam et al demonstrated the use of a novel device, Paediatric Perimeter for

objective quantification of visual fields in children with developmental delays (14 months to 6 year), which has a good potential to be explored in children with CVI (Satgunam et al., 2017).

1.5.8 Functional vision assessment

"Functional vision refers to how well an individual performs while interacting with the visual environment in their day-to-day activities"(Colenbrander, 2005). Functional vision assessment is important in many ways: (i) it is the closest parameter to real-world functioning (ii) simulates several visual functions simultaneously (for e.g. visual stimuli of varying sizes and contrast) (Bennett et al., 2019) (iii) easily understandable to the parents or other primary caregivers (iv) can be carried out in a non-clinical environment by clinicians as well as rehabilitation professionals. However, functional vision assessment protocols are usually not standardized and may not always be reproducible.

Simple day-to-day objects such as coloured balls, toys, lights of varying sizes and contrasting backgrounds are used as part of the functional vision assessment in children with ocular vision impairment (Lueck, 2004). The Bradford visual function box (BVFB) consisting of beads, books and toys of different sizes and colours is a good example. The BVFB was noted to be a reliable tool to assess children with complex disabilities when other standard visual function tools are challenging to use. The examiner needs to be alert to the child's responses to the objects which may vary from a change in pupil size, moving the eyes/head to locate the object and an attempt to reach out to the object of interest (Pilling et al., 2016). The near detection scale, similar to BVFB is yet another functional vision assessment tool that was found to be useful in measuring functional vision in children with severe to profound ocular vision impairment. Simple objects such as tinsel balls, cubes, sweeteners are used as part of this assessment tool (Salt et al., 2020).

For children with CVI, characteristics such as their visual attention, response to a visually cluttered environment, reaching out to visual stimuli (i.e., visually guided hand movements), colour preference, response to moving objects, visual field preference, light-gazing and non-purposeful gaze, response to visual reflex and response to visually novel objects should be noted. Roman-Lantzy has developed the CVI range instrument that includes all the parameters mentioned above, which are specific to CVI cohort above. Each of these characteristics have ratings and a cumulative score of the characteristics places the child on one of the 3 phases of CVI (equivalent to low, moderate or high functioning CVI) (Newcomb, 2010). This instrument is carried out through observation, parent interview and direct assessment. This instrument was used in this current study. Additional information about the CVI range instrument is discussed in section 5.6 (see appendix A14 for the complete instrument).

1.5.9 Visual perceptual tests

Visual perceptual skills such as visual attention, visual memory, visual orientation, visual sequential memory, motion perception, visual-motor integration, visual discrimination of form are all noted to be affected in children with CVI due to the dorsal and ventral stream dysfunction (Philip & Dutton, 2014). In one of the multi-centric studies carried out by the CVI prevalence study group, around 3% of children in mainstream schools were noted to have atleast one CVI-specific visual concern such as visual crowding, visual orientation and visual motor abnormalities, abnormal saccades and pursuits (Williams et al., 2021). Visual perceptual tests are commonly carried out in children with high functioning CVI (Brown & Yamamoto, 1986), as their visual concerns may not be explained by basic visual functions alone. Several tests of visual perception have been used to understand the perceptual visual impairment (PVI) in this cohort better. The most commonly used tests in children with CVI are summarized in table 1.4.

In addition to the tests mentioned above, several LEA cognitive assessment tools are also used commonly in clinical set-ups. Heidi expressions game to determine the child's understanding of facial expressions, LEA rectangle game to determine the child's size perception, LEA mailbox to ascertain the visual orientation and LEA 3D puzzle to understand any eye-hand coordination and matching issues that children with CVI are likely to have (LEA cognitive vision tests). The feasibility of using Sanet Vision Integrator, a computer-based diagnostic and therapeutic tool for enhancing vision perceptual skills in children with developmental delays has been demonstrated by Saha et al (Saha et al., 2023).

Test	**Visual perceptual skills measured**	**No. of persons tested**	**Age range tested**	**Key findings**
L94 visual perception battery (Ortibus et al., 2009)	Identification of everyday objects, visual constructional ability and form discrimination	75	4 to 20 years	Children with history of preterm birth and cerebral palsy were noted to have PVI
Developmental tests of visual perception (DTVP) (Fazzi et al., 2007)	General visual-perceptual quotient, nonmotor visual-perceptual quotient and a visual-motor integration quotient	27	4 to 15 years	88.9% had PVI Global reduction (all skills): 33.3%

Test	Visual perceptual skills measured	No. of persons tested	Age range tested	Key findings
Tests of visual perception-Revised (TVPS-R) (Ortibus et al., 2011a)	Visual discrimination, visual memory, visual spatial relationships, visual form constancy, visual sequential memory, visual figure ground and visual closure	25	Performance age: >6.5 years	Receiver operating characteristic curve for CVI questionnaire was 0.78 against TVPS-R
Children's visual impairment test (CVIT) (Vancleef et al., 2020)	Object Recognition, Degraded Object Recognition, Motion Perception, and Global-Local Processing	59	3-6 years	High correlation with L94 visual perception battery

Table 1.4: Commonly used tests of visual perception in children with CVI
(PVI: Perceptual visual impairment)

1.5.10 CVI Questionnaires

In several studies, structured history taking in children with CVI was noted through the use of questionnaires and were used as a screening tool to identify children at risk for CVI (Fazzi & Micheletti, 2020). Parents/caregivers opinion about the child's visual functioning is valuable and gives insights to aspects which could likely be missed in the short time spent in the clinics (McConnell et al., 2021). The questionnaires were answered by the parents/primary caregiver. Table 1.5 summarizes the most commonly used questionnaire in children with CVI.

In addition to the questionnaires mentioned in table 1.5, a 5-item scale derived from the original visual skills inventory was also noted to have excellent psychometric properties and therefore proposed as an easy screening tool (Gorrie et al., 2019). The use of paediatric quality of life inventory and (PEDsQL) (Mitry et al., 2016) and children's social behaviour questionnaire (CSBQ) (Geldof et al., 2015) has also been established in children with CVI.

Question-naire	No. of items	Domains	No. tested	Age range	Key findings
Visual skills inventory (Macintyre-Beon et al., 2012)	51	Visual fields, perception of movement, search, guidance of movement, attention, visual crowding and recognition and navigation	36	5 - 16.5 years	Helpful in characterizing high-functioning CVI
Insight inventory (Tsirka et al., 2020)	52	Visual search, visual fields, visual attention, perception of movement, visual guidance of movement and recognition/ navigation	51	5 - 16 years	Moderate correlations were noted with tests of visual perceptual skills
Flemish CVI questionnaire (Ben Itzhak et al., 2020)	46	Visual fixation, visual field, visual attention, familiarity, ventral and dorsal stream functions and other senses	511	3 - 6 years	An effective 5-factor model was determined to differentiate children with and without CVI
Strengths and difficulty questionnaire (SDQ) (Williams et al., 2021)	25	Hyperactivity, emotional symptoms, conduct problems, peer problems and prosocial scales	2217 teacher-reported and 714 parent-reported	5 years and 5 months - 11 years and 10 months	Was used as a screening tool to further assess children at risk for CVI in mainstream schools using tests of visual perception

Table 1.5: Commonly used questionnaires in children with CVI

1.6 Management of CVI

Although there are no evidence-based treatments for the resolution of CVI currently, a few causes of CVI are preventable. Neonatal hypoglycaemic brain injury which eventually causes HIE can be prevented by regular monitoring of the blood sugar levels of the neonates-at-risk (particularly if the mother has gestational diabetes) and also by ensuring regular feeds to the child, i.e., 10-12 times per 24

hours and by initiating the first feed early on, i.e., within 30-60 minutes of birth (Wight et al., 2014). Hypothermia therapy is an established procedure that was found to be effective in preventing cell death in HIE (Rocha-Ferreira & Hristova, 2016).

Co-existing ocular disorders should be managed effectively to enable the best use of residual vision, similar to those with ocular vision impairment. Refractive error was noted to be the single most important factor responsible for an improvement in the CVI grade (Jimenez-Gomez et al., 2022). Correction of refractive errors, strabismus and management of accommodative disorders are important components (Pehere et al., 2018), through near addition and/or orthoptic exercises, which may be feasible particularly in the high functioning group of CVI. Additionally, any existing ocular comorbidities (such as cataract, retinopathy of prematurity) should also be managed at the earliest possible opportunity.

A recent scoping review summarizing various interventions as part of managing CVI, identified published literature (n=23), such as case reports and original studies (including randomized controlled trials, n=3). The six key intervention areas identified were rehabilitative-based visual stimulation, task/environmental adaptations, vision skills training; medical/surgical-based acupuncture, stem-cell transplantation and one case study of transcranial electrical stimulation (Delay et al., 2023). Most of these studies were noted to have low-level evidence (Group OLoEW, 2011) and low critical appraisal scores (based on the JBI approach to critical appraisal checklists (Aromataris & Munn, JBI (2020)). Vision stimulation therapy (particularly for the low functioning CVI group) and visual skills enhancement therapy (particularly for the moderate and high functioning CVI group), is carried out as part of the early intervention therapies along with physiotherapy, speech therapy, occupational therapy, behavioural modifications and special education[3] to promote the child's overall development (Mojjada et al., 2022; Philip et al., 2022). However, high quality and controlled intervention studies are needed to establish evidence-based practices for managing children with CVI (Delay et al., 2023).

[3] *To help with academic-related concerns*

Key learnings

- CVI is the leading cause of paediatric vision impairment in developed countries and it is a rising cause in the developing world
- The most common causes of CVI include: HIE, NHBI and PVL
- CVI largely remains as the diagnosis of exclusion
- Commonly used diagnostic and assessment tests for children with CVI include: CVI questionnaires (structured history taking about the activity limitations and visual behavior), medical history, neuroimaging, comprehensive visual evaluation and clinical electrophysiology, developmental assessment, functional vision assessment and tests of visual perception

Chapter 2 : Clinical tools to assess visual acuity and contrast sensitivity in typically developing children and in children with special educational needs

2.1 Chapter overview

In the previous chapter, we had discussed briefly about the vision disorders and developmental delays in children with CVI and about the diagnostic and assessment tests used in children with CVI. However, the assessment of visual functions in children with SEN is more challenging than their typically developing counterparts due to limited cooperation (Salt & Sargent, 2014). Age-appropriate visual function tests may not always be sufficient to elicit responses from these children. Standardised tests for evaluating visual functions in this cohort currently do not exist as current tests have not been validated on this population given the heterogeneous nature of the different conditions under the spectrum of SEN. However, several studies have reported about the visual functions, common visual concerns and ocular abnormalities present in these children using various clinical tools (Salt & Sargent, 2014). In a recent systematic review by McConnell et al, the currently used vision assessment tests in children with CVI from 43 articles (McConnell et al., 2021) revealed that VA was noted in 93.5% of the studies. Whereas, the quantification of other parameters was as follows: visual fields (56.5%), CS (11.1%), stereopsis (15.6%), refractive status (43.5%) and accommodative status (8.9%) (McConnell et al., 2021). However, the quantifiable visual functions are primarily VA and CS due to the availability of tools in paediatric eye care. This chapter will describe the currently available and most commonly used VA and CS tools used in typically developing children and in children with SEN.

2.2 Visual acuity tests

Both resolution[4] *(i.e., "is the ability to resolve the critical element of a stimulus pattern such as the orientation of the gap in a Landolt C optotype")* (Holliman et al., 2019) and recognition acuity *(i.e., "the ability to identify a particular object")* (Holliman et al., 2019) can be used for quantifying VA in children with special needs based on their developmental age, unlike the typically developing paediatric population where the tests are based on their chronological age[5]. Resolution acuity tests can be carried out using electrophysiological methods such as VEP (see section 1.5.4) and behavioural methods as described below. Resolution acuity is based on the principle of preferential looking technique, this essentially means that the infant prefers to look towards a striped pattern/grating rather

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[4] The review paper on: Grating acuity tests for infants, young children and individuals with disabilities is published in Seminars in Ophthalmology. Full paper is available in appendix A1

[5] Chronological age refers to the age based on the date of birth and developmental age refers to the age that the individual is functioning at on a social, physical, intellectual, cultural and emotional level.

than a blank background of matched luminance (Atkinson et al., 1982). In this chapter, various VA tests based on behavioural methods that are commonly used in paediatric patients of varying ages will be discussed with special emphasis on testing children with SEN. The basic characteristics of all the resolution acuity tests has been summarized in table 2.2 and their clinical utility and repeatability indices, wherever available have been collated and presented in table 2.3.

2.2.1 Resolution acuity tests

Optokinetic drum

The optokinetic drum (figure 2.1) (Optokinetic drum (from Good-lite)) is considered to be the most rudimentary form of eliciting eye movements in infants. Optokinetic nystagmus movements are observed even in neonates under binocular viewing conditions (Braddick et al., 1996). However, weaker responses are elicited in nasal to temporal eye movements during monocular testing (Braddick et al., 1996). These directional movements are thought to originate from the cortical level which is immature in very young infants (1 to 3 months old) (Braddick, 1993), when assessed earlier in animal studies (Hoffmann & Schoppmann, 1975). Optokinetic nystagmus is elucidated using a cylindrical drum with vertical black and white gratings (Catford drum) (Suttle, 2001). This technique, however, has not been extensively used in children with SEN (Mackie & McCulloch, 1995). Wyngaarden et al studied the relationship between grating acuity and severity of developmental delay and found a moderate, but significant correlation ($p<0.5$) (Wyngaarden PA, 1991). A testing distance of 40 cms is used and the drum is rotated at a rate of about 1 revolution every 2-3 seconds (Optokinetic drum guide (Good-lite)).

Figure 2.1: Optokinetic drum

(Source: www.good-lite.com)

Teller acuity cards

The most commonly used resolution acuity tests use the preferential looking paradigm. This assessment technique has been noted to have good success rates. Table 2.1 is extracted from a review

article that had was published a quarter of a century ago, it summarizes the studies highlighting the usage of acuity card procedure using preferential looking technique and VEP in young children with various SEN (Mackie & McCulloch, 1995). A more recent review by our group includes the currently available commercial grating acuity tools currently and their various features and clinical utility indices (see appendix A1) (Sumalini & Satgunam, 2022). Our findings suggest that out of a total of 9 available preferential looking tests, 7 were paper-based and 2 were app-based tests. Five tests (TAC-II, LEA gratings paddle, Cardiff acuity cards Keeler acuity cards and PV app) had repeatability indices in typically developing young children and in heterogenous group of children with SEN (Sumalini & Satgunam, 2022). (tables 3.2 and 3.3)

Teller acuity cards (figure 2.2) developed by Davida Teller (Teller et al., 1986) are commonly used in younger children who are pre/non-verbal (Quinn et al., 1993) and those with delayed developmental milestones (Holmes & Coates, 1994). Normal TAC scores at ages of 4, 8, 11, 17, 24, 30 and 36 months were predictive of the normal acuity using TAC and HOTV test at 48 months. However, TAC scores below normal were noted to be less predictive (Mash & Dobson, 1998). Teller acuity cards is based on the 2-alternate forced choice preferential looking technique that is based on the seminal work of Fantz & Ordy (Fantz & Ordy, 1959). The age-based normative monocular and binocular acuities have been studied previously using the original TAC (Salomao & Ventura, 1995). However, in comparing the age-norms based on the original TAC (which is no longer available) with the modified and commercially available TAC (TAC-II) , it was noted that the acuity values obtained using the former cards needs to be adjusted to approximately 0.5 octave towards the lower acuity to be comparable to TAC-II (Clifford et al., 2005). The TAC-II (earlier available from Stereo optical and now from Precision Vision (Teller acuity cards (from Precision Vision)) includes 17 cards (25.5x55.5 cms) with a 4 mm peephole in the centre of the card for the examiner to view the child's response. Square-wave gratings are present on one side of the card with a grey background (with approximately 35% reflectance) on the other half. The range of spatial frequencies include: 0.23 (low vision card) 0.32, 0.43, 0.64, 0.86, 1.3, 1.6, 2.4, 3.2, 4.8, 6.5, 9.8, 13.0, 19.0, 26.0, and 38.0 cycles per centimetre (CPCM) and the blank card. The recent card set from Precision Vision does not include the 38.0 CPCM card (Teller acuity cards (from Precision Vision)). The recommended test distances include 38 cm, 55 cm and 84 cm. In case the examiner is unable to elicit the child's response even at 38 cm, the testing distance can be moved to as close as 19 cm and should be converted into appropriate cycles per degree (CPD). The TAC comes with a testing stage that is useful for mounting the cards and the stage covers other visual stimuli that can act as potential distractors (Reference and instruction manual: TAC-II., 2005). In the comparison of acuity estimates both with and without the testing stage in four

age groups (3.5, 11, 17 and 30 months), the age-appropriate VA norms were comparable among the age groups of 3.5, 11 and 30 months, however, the acuity scores obtained in children who were 17 months of age was reduced without the stage ($p<0.05$) (Clifford-Donaldson et al., 2006). Comparison of the inter observer agreement of acuities obtained using TAC in children with ocular or neurological disorders, or in combination with healthy preterm children revealed that the inter-observer agreement was within 1 octave or better in both the groups in 96% of the binocular test-retest comparisons, however children with ocular or neurological conditions may take up additional testing time (clinical group, average time taken=3.6±1.9 minutes; control group, average time taken= 2.4±0.6 minutes) (Getz et al., 1996). Teller acuity cards have also been used previously for measuring acuity in children with cerebral palsy with a good success rate (88%) having an age range between 3 to 109 months (Ipata et al., 1994).

Figure 2.2: Teller acuity cards-II with testing stage

Study	Method	Patients	Age ranges	Success (reliable acuity estimate)	Test/retest (within 1 octave)	PL & recognition (within 1 octave)	Results/comments
Morante et al 1982 (Morante et al., 1982)	FPL	n=30 pre term	34-40 weeks' gestation	90%	*	*	Subjects had significantly poorer results with PL and PP than normals ($p<0.001$)
Duckman and Selenow 1983 (Duckman & Selenow, 1983)	FPL	n=8 Down's n=4 mixed	6 months-3 years	92%	*	*	Presented as case histories
Mayer et al 1983 (Mayer et al., 1983)	FPL and OPL	n= 181 mixed	6 weeks-18 years	79%	*	*	63% 1 octave <normals mild 1.2-1.5 octave less moderate 2.1 octave less severe 3.2 octave less
Lennerstrand et al 1983 (Lennerstrand et al., 1983b)	OPL	n=26 mixed	5-24 years	81%	*	*	VA range 56-3.1 cycles/degree
Lennerstrand et al 1983 (Lennerstrand et al., 1983a)	OPL	n=8 mixed	4-19 years	87.5%	*	*	VA range >56-25 cycles/degree
Mohn and Van Hof-van Duin 1983 (Mohn & Van Hof-van Duin, 1983)	OPL and VEP	n=37 22 congenital 15 acquired	10 weeks-15 years	65%	*	*	PL and VEP performed on 7 patients VEP acuity <PL acuity in 75% of these
Dubowitz et al 1983 (Dubowitz et al., 1983)	FPL Fantz box Flash VEP	n=96 pre term		70%	*	*	Flash VEP on 13 patients close correlation between development of acuity as measured by PL and VEP
Jenkins et al 1985 (Jenkins et al., 1985)	FPL/OPL	n=25 mixed	2-15 years	84%	*	*	VA range 15-1 cycles/degree good predictor of VA<3.75 cycles/degree
Mohn and van Hof-van Duin 1986 (Mohn & Duin, 1986)	Acuity cards	n=24 developmental delay (mild) n= 19 mixed (severe)	21 months-12 years 16 months-22 years	98%	*	*	Mild-normal VA for age Severe below normal VA for age

Study	Method	Patients	Age ranges	Success (reliable acuity estimate)	Test/retest (within 1 octave)	PL & recognition (within 1 octave)	Results/comments
Mohn and van Hof-van Duin 1986 (Mohn & J., 1986)	FPL and OPL	n=19 developmental delay n=94 retarded	2 months-23 years	85%	*	*	Developmental delay - normal to within 1 octave of normal Retarded 1-2 octaves <normals
Hertz 1987 (Hertz, 1988)	Acuity cards	n=22 mixed n=6 profound	8-17 years	86% 67%	*	*	Interobserver variability within 1 octave when VA>0.2
Hertz 1987 (Hertz, 1987)	Acuity cards	n=33 Down's syndrome (mild) n= 19 cerebral palsy (severe)	7-20 years 22 months-7 years	97%B 85%M 100%	73% 47%	90%B 81%M (Down's syndrome only)	Down syndrome - range VA 48-4.2 cycles/degree
Birch et al 1987 (Birch et al., 1987)	OPL	n=20 cerebral palsy and developmental delay	15-194 months	100%	*	*	15% within normal limits 10% no threshold 20%>1 cycle/degree 55%<1 cycle/degree
Sebris et al 1987 (Sebris et al., 1987)	Acuity cards	n= 161 developmental delay and ocular disorders n=39 developmental delay controls	Mean 7.3 years Mean 11.2 years	90%B 86%M 92%B 85%M	*	*	
Hertz et al 1988 (Hertz et al., 1988)	Acuity cards	n= 11 mixed	2-26 years	82%	78%	*	VA range 15.6-0.18 cycles/degree
Hertz and Rosenberg 1988 (Hertz & Rosenberg, 1988)	Acuity cards	n=33 cerebral palsy (moderate)	2-7 years	87%	76%	*	VA range 45.6-0.18 cycles/degree

Study	Method	Patients	Age ranges	Success (reliable acuity estimate)	Test/retest (within 1 octave)	PL & recognition (within 1 octave)	Results/comments
Mohn et al 1988 (Mohn et al., 1988)	Acuity cards	n= 115 preterm n=35 mixed n=35 severe	- 14 weeks-12 years 14 months-12 years	97%B, 95%M 86%B 96%M 81%B 93%M	* * 89%	*	VA range 15-0.1 cycles/degrees low acuity for age VA range 8-5 cycles/degrees to no threshold
Orel-Bixler et al 1989 (Orel-Bixler et al., 1989)	Acuity cards and VEP	n=59 mixed	3-33 years	70%PL 95%VEP	*	66%	PL v VEP - better agreement with better acuity
Chandna et al (Chandna et al., 1989) 1989	(a) FPL and Snellen (b) FPL and Catford drum (c) FPL and Catford drum (mono)	n= 15 mixed n=40 mixed n= 15 mixed	29-83 years 24-81 years 29-82 years	100% 57.5% 32.5%CD 66.6% 33.3%CD	*	100%B 95%M (0 5 octave)	VA range 40-1 cycles/degree
Adams and Courage 1990 (Adams & Courage, 1990)	Acuity cards	n= 12 mixed (severe)	13 months-15 years	100%B 33%M	100%	*	VA range 40-2 cycles/degree
Schenk-Rootlieb et al 1992 (Schenk-Rootlieb et al., 1992)	Acuity cards	n= 164 mixed	6 months-19 years	91%	67-73%	*	VA range 30-6 cycles/degree 71% below visual norms
Hertz and Rosenberg 1992 (Hertz & Rosenberg, 1992)	Acuity cards	n=78 cerebral palsy (mild and severe)	18 months-8 years	99%	83% (mild) 72% (severe)	*	Mild VA range 26.1-7.8 cycles/degree Severe VA range 6-9-0-3 cycles/degree
Bane and Birch 1992 (Bane & Birch, 1992)	FPL and OPL	n=23 cerebral palsy, developmental delay, other	4 months-9 years	PL98% VEP 60%	* *	* *	PL VA> VEP VA in visually impaired; PL VA< VEP VA in controls

Study	Method	Patients	Age ranges	Success (reliable acuity estimate)	Test/retest (within 1 octave)	PL & recognition (within 1 octave)	Results/comments
Adams et al 1994 (Adams et al., 1994)	Acuity cards and contrast sensitivity	n=22 Down's syndrome	2-173 months	*	*	*	Acuity card estimates agree to within 1 octave with VA estimates from contrast sensitivity function
Courage et al 1994 (Courage et al., 1994)	Acuity cards	n=51 Down's syndrome	2 months-18 years	92%	*	*	94% had VA below expected mean VA for age
Getz et al 1994 (Getz et al., 1994)	Acuity cards	n=45 visual and neurology impaired preterms n=45 healthy preterms	3-38 months	*	93% 94%	*	Test time 4 (1.8) minutes Test time 2.6 (0.9) minutes
Mackie et al 1994 (Mackie et al., 1995)	Acuity cards and VEP	n=52 mixed	3-183 months	Acuity cards 85% VEP 88%	*	*	Acuity cards less successfully completed in the severely intellectually impaired

Table 2.1: Summary of studies using preferential looking techniques and visually evoked potential to assess visual acuity in children with special educational needs

(Extracted from Mackie RT and McCulloch DL, BJO, 1995)(Mackie & McCulloch, 1995)

*(*Data not reported, PL: Preferential looking, FPL: Forced-choice preferential looking, OPL: Operant preferential looking, VEP: Visual evoked potential, PP: Pattern preference, M=monocular test, B=binocular test, VA: Visual acuity)*

LEA gratings paddle-a preferential looking test

LEA gratings paddle (LEA GRATINGS: a Preferential Looking Test) (figure 2.3) is another frequently used grating acuity test in children using the preferential looking testing paradigm with established age normative data (Elgohary et al., 2017). The LEA gratings paddle does not use a testing stage and as a result is more portable and convenient to use. It consists of 4 paddles with 6 gratings and a solid grey background paddle. Each paddle is 20 cm in diameter. The acuity range that can be measured using LEA gratings include: 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 CPCM (cycles per centimetre of surface). Other than 57 cms, the recommended test distances include 28, 43, 85 or 115 cms as they are multiple or parts of 57 cms and therefore easy to calculate the CPD (as at 57 cms, 1 CPCM=1CPD) (Hyvarinen, 2018b).

Lea gratings and TAC-II have been found to have a close correlation (r=0.993, binocularly; r=0.991, monocularly) in infants from 5 weeks to 17 months of age (Yudcovitch et al., 2004). LEA gratings have also been successfully used in children with DS, hearing impairment and other cognitive impairments from 3 to 18 years of age (Gogri et al., 2015). The inter-observer agreement for both binocular and monocular testing was noted to be within 0.5 octave for 94.2% of observations (Deshmukh et al., 2020).

Figure 2.3: LEA gratings paddle- preferential looking test

Ohio State University Newborn Acuity Chart

Ohio State University Newborn Acuity Chart (figure 2.4) (Ohio State University Newborn Acuity Charts (from Precision Vision)) were developed by Angela M Brown in 1986 (Brown & Yamamoto, 1986). The grating acuity was successfully measured in normal, preterm new-born and full-term new-born infants with no ophthalmologic abnormalities. The acuity cards were found to be simple, reliable,

fast with about 89% success rate for testability[6] (Brown & Yamamoto, 1986). The cards have also been used in children with SEN (for e.g. CVI, retinopathy of prematurity with developmental delays) by our group and were noted to have a test-retest repeatability of < 1 octave (i.e., acuity difference: -0.2±0.56 $\log_2$CPD, 95% limits of agreement were -1.29 to 0.89 $\log_2$CPD) *(unpublished results, manuscript in progress).*

Figure 2.4: Testing grating acuity using the Ohio State University Newborn Acuity Chart

(Note: Photo consent obtained from the parent)

Keeler acuity cards

Keeler acuity cards measure grating acuity and follows the 2-alternate forced choice preferential looking paradigm and are used predominantly in the European countries (KAC children's grating test card set (from Good-lite)). Monocular acuities in children aged 1-6 years were found to be comparable between Teller acuity and the Keeler acuity cards (children's additional set) (Neu & Sireteanu, 1997). However, the spatial frequencies of both sets of cards are not identical (Neu & Sireteanu, 1997). Keeler acuity cards are available in 2 sets, namely the 'Infant assessment set' and 'Children's additional set'. Both the sets have cards with the following dimensions: 26.5x57.5 cms made of plastic composite for durability. Each card contains 2 circles with a diameter of 10.3 cms and having a white border of 1 mm thickness. One of the circles has the gratings while the other circle has homogenous grey background as the card (figure 2.5). The examiner views the child's response through the central peephole.

The infant assessment set consists of 7 cards plus one blank card. Acuities in the range of 0.18 to 12.5 CPD can be measured at 38 cms testing distance. For children beyond 1 year of age, the children's

[6] *The ability of an individual to complete a test*

additional set is used. The children's additional set can be used for children from 1 to 6 years of age. There are 10 cards in this set and the spatial frequencies range from: 0.3 to 35.4 CPD tested at 38 cms. When compared to Cardiff acuity cards, the 95% LoA between both the tests were noted to be: ±0.5 logMAR in children with neurological impairment (8 months to 19 years) (Mackie et al., 1996).

Figure 2.5: Keeler acuity cards

City-Cardiff preferential looking acuity test

The City-Cardiff preferential looking acuity test also presents gratings enclosed in a circle similar to the Keeler acuity cards (figure 2.6). The cards have been developed by a team of clinical vision scientists from City, University of London and Cardiff University, UK. The cards are available in a flip format, as a result it is easily portable. The cards can be placed on the 'A' shaped display stand that avoids the distraction of the examiner holding the cards. There are 17 cards (2 cards per spatial frequency) that range from 2.0 logMAR (0.3 cycles per degree) to -0.1 logMAR (38 cycles per degree). The dimensions of the cards are: 22.2x30.2 cms, circle diameter: 7.45 cms). The recommended testing distance is 50 cms.(City-Cardiff preferential looking acuity test set (from Good-lite)) The grating acuity notations are provided in all three notations: logMAR, Snellen fraction and CPD. The clinical utility of these cards is yet to be established as no studies have reported the use of these cards till date.

Figure 2.6: City-Cardiff preferential looking acuity test

Patti stripes

Patti stripes consists of six square-wave gratings that range from 0.3 to 9.6 CPCM. The gratings are printed on either side of the three paddles and one more paddle consisting of solid grey (blank) background that are square shaped (dimensions: 17.8 X 32 cms) (figure 2.7). The three recommended test distances are 25, 50 and 100 cms. The paddles are made of plastic (4 mm) and are very durable (Patti stripes square wave 4 grating paddles (from Precision Vision)). Similar to LEA gratings, equal movement of both the paddles (blank and the grating) should be made during testing. The clinical utility of these cards is yet to be established as no studies have reported the use of these cards till date.

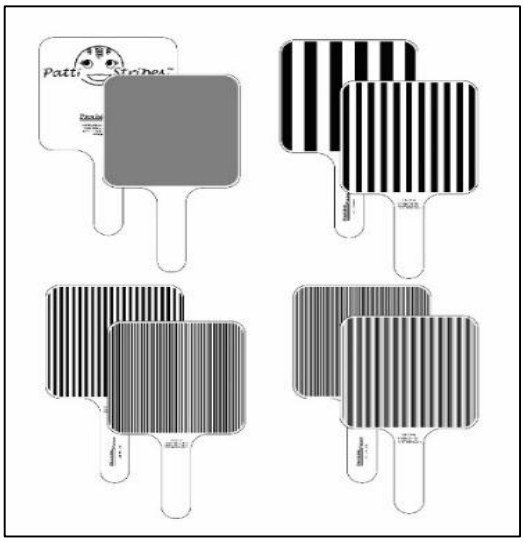


Figure 2.7: Patti stripes

(reprinted with permission from the website)

Peekaboo Vision application (PV app)

Peekaboo Vision (figure 2.8) is a digital-tablet based interactive application that has been developed to be used on an iOS platform to measure grating acuity in children, using preferential looking testing paradigm (Livingstone et al., 2019). The test has an interactive video feedback of a green cartoon popping up along with a 'yippee' audio on correct click response to engage the children during the test procedure. The tool's reliability indices were found to be comparable in two different settings to the Keeler acuity cards (study 1-Malawi; the mean acuity difference between PV app and Keeler acuity cards= 0.02 logMAR, 95% limits of agreement (LoA)= 0.33 to 0.37 logMAR; study 2-United Kingdom; the mean acuity difference between the PV app and Keeler acuity cards= 0.01 logMAR, 95% LoA= -0.413 to 0.437 logMAR) (Livingstone et al., 2019). The clinical utility and reliability indices of the PV app have been studied in children with DS and compared with TAC-II. The acuity differences were found to be significantly different between both tools (i.e., mean acuity difference: –

0.44 ± 0.38 logMAR (95% LoA: –1.18 to 0.3). A coefficient of repeatability (CR) of 0.35 logMAR was recorded using the PV app in a small subset of children with DS (see appendix A3) (Sumalini et al., 2022).

Figure 2.8: Peekaboo Vision application

Cardiff acuity cards

The Cardiff acuity test (figure 2.9) designed by Margaret Woodhouse (Cardiff acuity tests (from Kay pictures)) (Cardiff Pediatric Acuity Test (from Good-lite)) has been developed for assessing children in the age range of 6 months to 3 years and also for adults with stroke, cognitive impairment and dementia. It follows the principle of preferential looking technique and uses pictures as vanishing optotypes (Fariza et al., 1990; Frisen, 1986). The paediatric test consists of a pack of 36 cards with six pictures (fish, train, dog, house, duck and car). To recheck the acuity at the same acuity level, the same optotype with similar spatial frequency is shown on three consequent cards with change in the position of the picture (either up or down). The picture outline is marked by a white band and has two black bands as the borders. The recommended testing distances are at 100 or 50 cms. The average luminance of the picture outline approximately matches the card's background. The pictures include spatial components that are complex in nature and may not be comparable to the grating acuity across all the spatial frequencies (Charman, 2006). However, comparable acuities were obtained using Cardiff acuity cards for children with and without cognitive or physical disabilities when compared with TAC at high confidence level and poor agreement was observed at low confidence level for both tests (Adoh et al., 1992). Acuity estimates using Cardiff acuity cards were not sensitive to visually significant refractive errors when compared to TAC in children aged 2 years and under (Sharma et al., 2003). The 95% LoA was noted to be : ±0.5 logMAR for Cardiff acuity cards and Keeler acuity cards in children with neurological impairment (8 months to 19 years) (Mackie et al., 1996). In comparison with TAC-II in children with visual, auditory, motor and cognitive impairments, the mean acuities of Cardiff acuity cards were noted to be comparable (p=0.068). However, the 95% LoA of agreement for repeatability

was ±0.60 logMAR for TAC II and ±0.70 logMAR for Cardiff acuity test. A higher variability was noted in children with poorer acuity for Cardiff acuity test (Johnson et al., 2009).

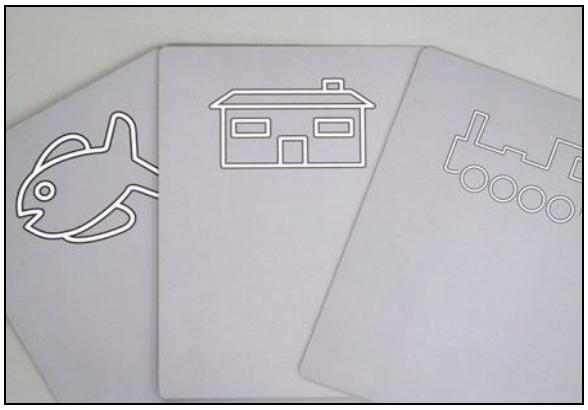


Figure 2.9: Cardiff acuity cards
(Source: www.good-lite.com)

Automated visual acuity test (AVAT)

The development of AVAT was recently published (figure 2.10) (Vrabic et al., 2021). This automated testing is based on the preferential looking technique and requires a minimally skilled examiner and was found to be testable even in children as young as 5 months of age. The testing equipment consisted of an eye tracker (remote eye tracker Tobii Pro X3-120 (Tobii AB, Stockholm, Sweden) that was set below 15.6-inch LCD screen (laptop HP Zbook G5). A sampling rate of 120 Hz was used to record the binocular gaze data. A 5-point binocular calibration was used. Nine grating acuities ranging from 2.0 to 0.3 logMAR were presented on the computer screen in a 2-alternate forced choice paradigm. There are six different layouts of the circle across the screen. The testing distance was set at 64-66 cms. Two circles of diameter 70 mm (with 1 mm border thickness) were placed on the grey background (330 × 185 mm) for the presentation. The distance between the centers of the 2 circles was maintained at 112 mm and the placement of the circles were set at 11 mm from the upper and lower background borders and 37 mm away from lateral (Vrabic et al., 2021).

The agreement between the acuity estimates obtained with AVAT and conventional tests like Keeler acuity cards for the preverbal group and LEA symbols for the verbal cohort was found to be fair with the Lin's concordance coefficient of 0.53 (95% confidence intervals: 0.31 to 0.72). However, an overestimation of acuity with AVAT was noted for children who had >0.4 logMAR using the conventional tests and underestimation for those whose acuity was ≤0.4 logMAR (Vrabic et al., 2021).

Figure 2.10: Grating acuity testing using Automated Visual Acuity Test
(reprinted with permission from the publishers)

Test name	**Number of gratings/cards**	**Spatial frequency range**	**Recommended test distances**
Teller acuity cards-II	15+1 blank card	0.23 to 38.0 CPCM	9.5, 19, 38, 55 and 84 cms
LEA gratings preferential looking test	6+1 blank card	0.25 to 8.0 CPCM	28, 43, 57, 85 and 115 cms
Ohio State University Newborn acuity chart	10+1 blank card	0.062 to 1.515 CPD	38 and 57 cms
Keeler acuity cards	8 infant assessment cards 10 children's additional set	Infant assessment cards: 0.18 to 12.5 CPD Children's set:0.3 to 35.4 CPD	38 cms*
City-Cardiff preferential looking acuity test	17+1 blank card	0.3 to 38 CPD	50 cms
Patti stripes	6+1 blank card	0.3 to 9.6 CPCM	25, 50, 100 cms
Peekaboo Vision application	18 spatial frequencies can be tested at any given distance in the range of 25-50 cms	2.21 to -0.18 logMAR	25 to 50 cms
Cardiff acuity cards	36	20/160 to 20/12.5 (3.75 to 48 CPD)	100 or 50 cms
Automated visual acuity test	9	0.29 to 14.5 CPD	64-66 cms

Table 2.2: Summary of the basic specifications of currently available grating acuity tests
**One study reports using longer working distances of 55 and 84 cms also (Neu & Sireteanu, 1997)*

Test name	Study	Cohort	Age range	Acuity ranges obtained	Testability rate (%)	Testing time	Repeatability	Remarks
Teller acuity cards-II	Clifford et al (Clifford et al., 2005)	Infants and children with no ocular problems (n=60) 3.5-month-old, n=20 11-month-old, n=20 30-month-old, n=20	3.5-30 months	Overall, across all the ages: 0.47 octave better with TAC as compared to TAC-II At 3.5 months: 0.2 octave At 11 months:0.4 octave At 30 months: 0.7 octave	87%	-	-	Acuity estimates obtained by TAC-II are lower as compared to TAC and need to be adjusted by approximately 0.5 octave
	Johnson et al (Johnson et al., 2009)	Children with multiple sensory, visual, auditory, motor and/or cognitive impairments (n=20)	5-21 years	Mean=-0.09 to 1.85 logMAR (median:0.81 logMAR)	95%	204 ± 111 s	±0.6 logMAR	Comparable acuity estimates with Cardiff acuity cards
	Qiu et al (Qiu et al., 2011)	Normal infants (n=244)	5-24 months	Mean acuity across all age ranges: B/O: 0.17 to 0.83 decimal; M/O:0.15 to 0.8 decimal	B/O:98.7% M/O:89.2%	Tests completed within 2 to 5 min	-	All children reached adult-like acuity of 26 CPD at 24 months of age

Test name	Study	Cohort	Age range	Acuity ranges obtained	Testability rate (%)	Testing time	Repeatability	Remarks
Teller acuity cards-II	Leone et al (Leone et al., 2014)	Typically developing children (n=1404, total; TAC-II on n=544, B/O; n=442, M/O)	6 to <42 months	Mean acuity ranges (95% prediction limits): from 6 to <9 months: B/O: 6.33 (3.57–11.20) CPD; SD: 0.41 octave to ≥33 months: 12.60 (5.53–28.73) CPD; SD:0.58 octave from 6 to <9 months: B/O: 5.72 (2.78-11.76) CPD; SD: 0.52 octave to ≥33 months: 11.81 (5.04–27.7) CPD; SD:0.59 octave	B/O: 94% M/O: 76%	-	-	Significant improvement in acuity estimates were noted with age: r^2:0.29, p<0.0001, B/O; r^2:0.32, p<0.0001, M/O
	van der Zee et al (van der Zee et al., 2017)	Typically developing school children (n=60) Children with ocular abnormalities (n=21) Children with suspected brain damage (n=26)	3-12 years	Median Snellen equivalent Typically developing: 20/11.6 Ocular abnormalities: 20/17.5 Suspected brain damage: 20/11.6	Typically developing:98.3%; Ocular abnormalities:71.4%; Suspected brain damage:92.3%	-	-	Crowding ratio was noted to be a better indicator than visual acuity to detect children at risk of cerebral visual impairment

Test name	Study	Cohort	Age range	Acuity ranges obtained	Testability rate (%)	Testing time	Repeatability	Remarks
	Xiang et al (Xiang et al., 2021)	Normal infants and toddlers (n=218)	Birth-36 months	Mean acuity ranges (lower to upper limit) from 2-3 months: B/O: 1.18 (0.41 to 3.42) CPD to 34-36 months: 12.01 (3.1 to 46.5) CPD; from 2-6 months: M/O: 1.97 (0.55 to 7.06) CPD to 34-36 months: 10.75 (4.75 to 24.34) CPD	B/O: 98.6% M/O: 50.2%	-	-	Normative visual acuity norms for infants and toddlers from southern China
LEA gratings paddle	Martini et al (Martini et al., 2014)	Normal infants (n=133)	<4 months	At 1 month: 0.55 ±0.70 CPD At 2 months: 1.35 ±0.69 CPD At 3 months: 3.11 ±0.54 CPD	-	-	-	Acuities measured across 3-month to follow-up. Significant differences in acuities across the 3 months
	Deshmukh et al (Deshmukh et al., 2020)[#]	Preverbal (<3 years) and older nonverbal children (with developmental delay) (n=31)	4-44 months	Mean B/O acuity: 2.07CPD±1.34 octave; Mean M/O acuity (RE): 0.98 CPD±1.96 octave; Mean M/O	B/O: 100% M/O: 72%	-	Inter-observer agreement (for B/O and M/O): within 0.5 octave for 94.2% observations	-

Test name	Study	Cohort	Age range	Acuity ranges obtained	Testability rate (%)	Testing time	Repeatability	Remarks
LEA gratings paddle				acuity (LE): 0. 89 CPD±1.61 octave				
	Mody et al (Mody et al., 2012)	Normal children (n=200). Unilateral strabismic or anisometropic amblyopic group (n=30)	6 months-3 years	B/O: 1.0 ± 0.6 logMAR (range: 0.5 - 2.1) M/O: 1.15 ± 0.15 logMAR (range: 0.88 - 1.48)	-	B/O:26.5 ± 5.0 s (range: 20 - 50) M/O: 23.1 ± 4.6 s (range: 20 -50)	-	Better acuity estimates were noted with Cardiff acuity cards as compared to LEA gratings
	Yudcovitch et al (Yudcovitch et al., 2004)	Infants and toddlers (including 2 with preterm births)	5 weeks to 17 months	Mean B/O acuity at 0–4 months:3.8 CPD; 12-16 months of age:10.2 CPD Mean M/O acuity at 0–4 months:2.7 CPD; 12-16 months of age:10.4 CPD	-	-	-	Strong correlation between TAC and LEA gratings (r=0.993, B/O; r= 0.991, M/0). Intrasubject correlation between both tests were: r=0.505, B/O; r=0.615, M/O
Ohio State University Newborn acuity chart	Brown et al (Brown et al., 2018)	Healthy newborn infants (experiment 1, n=47; experiment 2, n=22)	Newborn infants (median birth age: 1 day, 95%:<2 days)	Range: B/O: 0.783 to 1.204 CPD	-	-	-	Psychophysical methods were primarily tested: method of constant stimuli and descending method of limits
Keeler acuity cards	Livingstone et al (Livingstone et al., 2019)	Typically developing children with	2-60 months	Median acuities: Study 1: 0.4 logMAR	Study 1: 90.8% Study 2: 95.5%	-	Study 1: 95% LoA of -0.427 to 0.323 logMAR	Study 1&2: Repeatability was found to be

Test name	Study	Cohort	Age range	Acuity ranges obtained	Testability rate (%)	Testing time	Repeatability	Remarks
Keeler acuity cards		and without visual problems (n=58, study 1; n=60, study 2)		(range: 0.1 to 1.6 logMAR) Study 2: 0.3 logMAR (range: 0.1 to 0.9 logMAR)		B/O: 251 s	(CR=0.37) Study 2: 95% LoA of -0.432 to 0.407 logMAR (CR=0.42)	similar for binocular and monocular viewing conditions
	Neu & Sirteanu (Neu & Sireteanu, 1997)	Typically developing children (n=95)	7-78 months	Mean acuities (CPD) M/O: 19-35 m:14.5±4.4 36-47 m: 25±7.2 48-59 m: 26.2±8.3 60-71 m: 29.1±8.4 72-78 m:31.4±11.9	98.9%	-	-	Was found to have comparable age norms as measured with TAC
	Mackie et al (Mackie et al., 1996)	Children with neurological impairment (n=91)	8 months-19 years	Range:0.0 to 2.2 logMAR	91%	-	-	95% LoA: ±0.5 logMAR when compared with Cardiff acuity cards
Peekaboo Vision application	Livingstone et al (Livingstone et al., 2019)	Typically developing children with and without visual problems (n=58, study 1; n=60, study 2)	2-60 months	Median acuities (for all children): Study 1: 0.5 logMAR (range: 0.1 to 1.9 logMAR) Study 2: 0.2 logMAR (range:-0.18 to 0.9 logMAR)	Study 1: 93.6% Study 2: 94.9%	- B/O:185 s	Study 1: 95% LoA of -0.283 to 0.198 logMAR (CR=0.27); Study 2: 95% LoA of -0.413 to 0.437 logMAR (CR=0.32)	Study 1: Repeatability was found to be slightly poorer for binocular viewing condition compared to monocular Study 2: Similar repeatability

Test name	Study	Cohort	Age range	Acuity ranges obtained	Testability rate (%)	Testing time	Repeatability	Remarks
Peekaboo Vision application								indices noted for both viewing conditions
	Sumalini et al (Sumalini et al., 2022)	Children with Down syndrome (n=37) and age-matched controls (n=28)	Down syndrome (1.3 to 17 years), controls (2.3 to 15 years)	Mean acuities: 0.16 ± 0.34 (Down syndrome), –0.13 ± 0.12 (controls)	97.2% (Down syndrome), 100% (controls)	1.8±0.8 min (Down syndrome), 1.17±0.38 min (controls)	95% LoA: -0.14 to 0.4 logMAR, CR: 0.35 (Down syndrome), 95% LoA: -0.37 to 0.33 logMAR, CR: 0.33 (controls)	Significant difference in acuities with TAC-II in children with Down syndrome: 95% LoA: -0.5 to 0.4 logMAR, CR: 0.43 and controls: 95% LoA: -0.1 to 0.1 logMAR, CR: 0.08
Cardiff acuity cards	Mackie et al (Mackie et al., 1996)	Children with neurological impairment (n=91)	8 months-19 years	Range: 0.0 to 1.3 logMAR	89%	-	-	95% LoA: ±0.5 logMAR when compared with Keeler acuity cards
	Johnson et al(Johnson et al., 2009)	Children with multiple sensory, visual, auditory, motor and/or cognitive impairments (n=21)	5-21 years	Mean logMAR: 0.72±0.47	95%	222±111 s	±0.7 logMAR	Higher variability noted with poorer acuity using Cardiff acuity cards
Automated visual acuity test (AVAT)	Vrabic et al(Vrabic et al., 2021)	Healthy children (n=36)	5 months-16 years	-	97%	Was set for 3 min + 24 s	-	Acuity overestimation with AVAT was observed for

Test name	Study	Cohort	Age range	Acuity ranges obtained	Testability rate (%)	Testing time	Repeatability	Remarks
								>0.4 logMAR on standard tests and underestimation on AVAT for ≤0.4 logMAR on standard tests. Less sample in <3 years group (n=4). Standard tests included in the study: Keeler acuity cards and LEA symbols.

Table 2.3: Clinical utility indices of available resolution acuity tests collated from different studies

(Adapted from (Sumalini & Satgunam, 2022))
(B/O=binocular, M/O=monocular, s=seconds, min=minutes, MAR=minimum angle of resolution, CPD=cycles per degree)
**The search results of Teller acuity cards-II have been given*
[#]The acuity estimates of only observer 1 have been given

2.2.2 Recognition acuity tests

Table 2.4 summarizes the basic specifications for the commonly used recognition acuity tests among children

LEA symbols and number chart

LEA symbol optotypes (figure 2.11a) (LEA SYMBOLS® 10 Line Distance Chart (from Good-lite)) have been extensively used in the paediatric age group to measure recognition acuity (Becker et al., 2000; Cyert et al., 2003; Hered et al., 1997). The LEA symbols chart uses four optotypes (an apple, ball, square and house) and has been developed and validated by Lea Hyvarinen (Hyvarinen, edited in July 2009). These four symbols have been chosen because they have defined end points and appear similar when blurred or beyond the acuity threshold. The test can be administered either through naming or matching the optotypes using the demonstration card. LEA symbols have been compared with various other charts such as HOTV (Hered et al., 1997), ETDRS (letter optotypes) (Dobson et al., 2009) and Patti pictures (Mercer et al., 2013) and was found to be an efficient test measure in young children. These optotypes have been widely used in Special Olympics screening as part of the Opening eyes program for assessing both distance and near VA of athletes (Gothwal et al., 2017; Woodhouse et al., 2003). Success rates of testability of up to 70% was observed in typically developing young children (age range: 21 months to 7 years) and up to 97.8% in children and adults (age range: 9 to 69 years) with intellectual disability using LEA symbols (Becker et al., 2000; Woodhouse et al., 2003).

The chart is also available with number optotypes (figure 2.11b) (LEA numbers 15-line distance charts (from Good-lite)). This test is intended primarily to be used in assessing visual acuity in ≥ 5 years children with special educational needs. The acuity range that can be measured includes: 20/200 to 20/8 and is recommended to be used at 3 metres (LEA numbers 15-line distance charts (from Good-lite)). In a study measuring the acuity of adults at different distances using the LEA numbers and symbols, the number chart was noted to have similar acuities at all distances and no clinically significant difference (<2 optotypes) was noted for LEA symbols (Hing et al., 2007). The number optotype is also available as LEA numbers low vision book that can test an acuity range between 20/1600 to 20/16 (LEA numbers low vision book (from Good-lite)).

Figure 2.11: LEA symbols chart with key card (a) and LEA number chart (b)

(Source: www.good-lite.com(LEA numbers 15-line distance charts (from Good-lite); LEA SYMBOLS® 10 Line Distance Chart (from Good-lite))

Kay pictures

The Kay pictures VA test (The Kay Picture Test) is the most commonly used test among typically developing pre-literate children of 2-3 years of age (Milling, 2015). It is available as a single and linear crowded book and also has a low vision book and a separate screening book and also as an application. The matching card is available for all the acuity books. The new crowded log-MAR Kay pictures book has 5 boxes per row and measures an acuity range of 0.70 logMAR to -0.2 logMAR (i.e., 20/100 to 20/12.5). The testing distance is at 3 metres. While the single crowded book can be used for children as young as 18 months and above, the linear crowded book is suitable for children of 30 months and above (Kay Picture Test Linear Crowded Book). The six optotypes used for the testing includes: an apple, star, house, duck, boot and van (figure 2.12). These pictures have been chosen following four phases of testing and comparison with logMAR VA assessment charts such as LEA symbols, ETDRS and Landolt C (Milling, 2015). Kay pictures was noted to produce better VA readings when compared with the standard ETDRS chart in 30 adults with ocular pathology and in 40 children with amblyopia, with similar test-retest repeatability measures between both charts (± 0.14 logMAR for adults and ± 0.16 logMAR for children) (Shah et al., 2012).

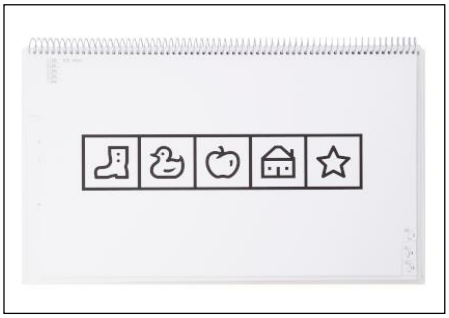


Figure 2.12: Picture optotypes used in Kay picture test

(Source: www.kaypictures.co.uk)

Sheridan Gardiner and Modified Sheridan Gardiner

Sheridan Gardiner (figure 2.13) (Sheridan Gardiner Child Acuity Test (from Keeler)) is one of the most commonly used recognition test in preschool (typically developing children of 3 -5 years) children (Omar et al., 2012). It a revised version of the STYCAR letter test and has been developed by Sheridan and Gardiner (Sheridan & Gardiner, 1970). The seven optotypes A, U, X H, O, T, V that are used in this chart, following the Snellen principles. These optotypes are easily recognizable and vertically symmetrical (Paul & Sathyan, 2018). The testing distance is usually at 6 metres and the child is asked to match the optotype on the key card. Sheridan Gardiner charts were found to yield better VA results than a new Rader (broken wheel test) (Mildenberger et al., 2004). In preschool vision screening, Sheridan Gardiner was noted to consume lesser testing time when compared to LEA symbols ($p < 0.001$ for both right and left eyes). The test was also noted to have better specificity (83.33%; 95% CI: 70.12%–91.30%) and better positive predictive value compared to LEA symbols (66.67%; 95% CI: 90.26%–97.30%) for screening typically developing preschool children. However, the Sheridan Gardiner was noted to have poorer sensitivity (52.63%; 95% CI: 45.29%–59.8%) when compared to LEA symbols (94.74%; 95% CI: 70.13%–81.06%). Therefore, the authors concluded that the latter was better for the preschool vision screening purposes (Paul & Sathyan, 2018). The linear letters with crowding are often used for screening amblyopia in young children (Williams et al., 1995).

Figure 2.13: Sheridan Gardiner chart
(Source: www.keelerusa.com)

A modification of the single optotype of Sheridan Gardiner test is the Cambridge crowding cards that can be used at either 3 or 6 metres. In this the target letter is surrounded by 4 other letters. (figure 2.14). Atkinson et al demonstrated that the crowding effect of these cards at 3 metres was similar to that of the crowding effect at 6 metres (Atkinson et al., 1988).

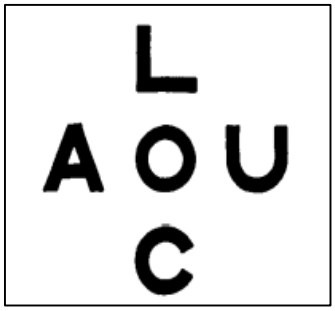


Figure 2.14: An example of a crowded letter from Cambridge crowded cards
(Extracted from: Atkinson et al, 1988(Atkinson et al., 1988))

HOTV test

The HOTV test is a revised version of the Sheridan Gardiner test and has only 4 letters: H, O, T and V that are vertically symmetrical (HOTV distance folding pediatric eye chart (from Good-lite)). (figure 2.15) This chart is available as single optotype test with crowded bars (HOTV crowded response panel (from Good-lite)), proportionately-spaced (HOTV pediatric eye chart for the wall (from Good-lite)) and linear-spaced letters (HOTV linear-spaced distance chart (from Good-lite)). There is a key card that the child can use to match the letters if verbal response is limited. The chart is calibrated for 3 metres and measures an acuity range from 20/200 to 20/10. Good testability rates have been reported using the single optotype of this test with crowding bars on 4 year olds (87%) and 5-7 years old (96%) by the Amblyopia Treatment Study group (Holmes et al., 2001). The test-retest repeatability also was found to be good, i.e., within 93% of the eyes were within 0.1 logMAR (Holmes et al., 2001), which was similar to that of the adults on ETDRS chart (Rosser et al., 2003). In a large cohort (n=777) of pre-school children in the age-range of 3-5 years, both HOTV and LEA symbols were found to have similar reliability indices, however, the testability of 3 year olds was better with LEA symbols (92% versus 85%, $p = 0.05$) (Hered et al., 1997).

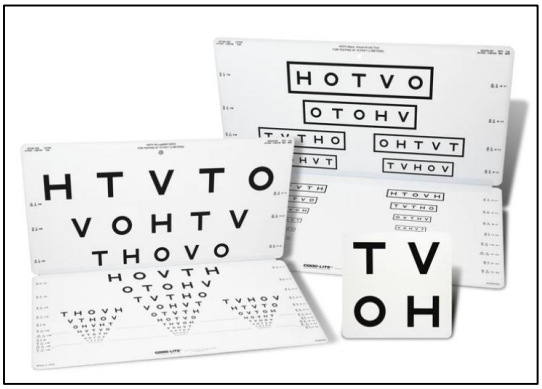


Figure 2.15: HOTV distance folding paediatric charts along with key card
Source: www.good-lite.com(HOTV distance folding pediatric eye chart (from Good-lite))

Patti pics

Patti pics includes 5 optotypes, i.e., apple, ball, house, square and star (Patti pics (from Precision Vision)) (figure 2.16). The chart is calibrated for 3 metres and the acuity range that can be measured ranges from 20/125 to 20/8. Visual acuity values obtained using Patti pics were found to be comparable to that of Sloan letters in older children as well as in adults (Mercer et al., 2013).

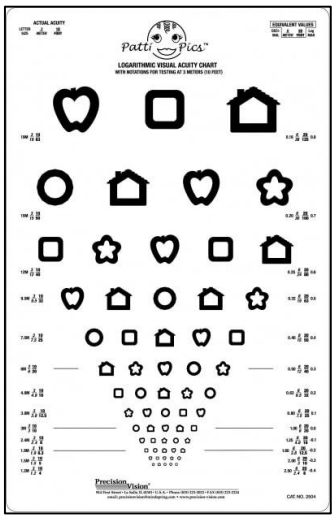


Figure 2.16: Patti pics chart
(Source: www.precision-vision.com)

Letter charts

Letter charts are available as ETDRS charts (What is ETDRS? (from Precision Vision)), Bailey-Lovie high contrast visual acuity charts (Bailey-Lovie chart set (from Precision Vision)), Computerized logarithmic charts (e.g., COMPlog) (About COMPlog) (figure 2.17). These charts are considered standardized as they have been validated in both children and adults. The Paediatric Eye Disease Study (PEDIG) group use the standard ETDRS chart in several amblyopia studies in

children of age 7 years and older (Chen & Cotter, 2016). However, the challenge for carrying out the acuity measurement using these optotypes in children with special educational needs is their unfamiliarity with letters. Abu Bakar and Chen found that in a group of children with heterogeneous causes of special educational needs, the testability with modified ETDRS chart was poor (56%) (Abu Bakar & Chen, 2014). In addition to the charts mentioned above, Thomson test charts (Thomson Software Solutions, 2016) are computerized charts that are available in both logMAR and Snellen design and have the availability of several optotypes to choose from.

(a) (b) (c)

Figure 2.17: Letter optotype charts: (a) ETDRS chart (b) Bailey-Lovie high contrast chart and (c) COMPlog chart

(Source: www.good-lite.com, www.precision-vision.com)

Test name	Type of optotypes	Spatial frequency range	Recommended test distances
LEA symbols/number	Apple, ball, square and house/numbers	20/125 to 20/8 // 20/200 to 20/8	3 metres
Kay pictures	Apple, star, house, duck, boot and van	20/100 to 20/12.5	3 metres
Sheridan Gardiner/modified Sheridan Gardiner	A,U,X,H,O,T and V/same letters with 4 other letters as distractors	20/200 to 20/20	6 metres/3 or 6 metres
HOTV test	H, O, T and V	20/200 to 20/10	3 metres
Patti pics	Apple, ball, square, house and star	20/125 to 20/8	3 metres
Letter charts *ETDRS* *COMPlog* *Bailey-Lovie high contrast chart*	 Sloan letters Sloan letters Non-serifed letters	 20/200 to 20/10 20/796 to 20/10 20/125 to 20/6.3	 4 metres 1.5-7 metres 6 metres

Table 2.4: Summary of the basic specifications of currently available commonly used paediatric recognition acuity tests

(ETDRS: early treatment diabetic retinopathy study, COMPlog: computerized logarithmic chart)

2.4 Contrast sensitivity charts

Contrast sensitivity is an important clinical parameter for accomplishing functional vision tasks in activities of daily living and is considered as an important parameter influencing the quality of life (Rosenberg & Fischer, 2014). Good et al had noted spatial CS vision loss in children with CVI by using sweep parameter visual evoked potential (Good et al., 2012). However, CS is not commonly used in the vision examination protocol (Xiong et al., 2020) due to lack of awareness among clinicians about the importance of this measure and the lack of tests in the general eye examination set-up. Contrast sensitivity can be measured using gratings and optotypes such as pictures (Hiding Heidi cards, Mayer-Kran Double-Happy low contrast test), symbols (LEA low contrast flip chart), letters (Pelli Robson contrast sensitivity test, Mars letter contrast sensitivity test), numbers etc. Alternatively, low contrast acuity is tested commonly in the low vision clinics with charts such as the Bailey-Lovie low contrast chart.

In addition to the above-mentioned contrast sensitivity tests, the grating CS tests include the Vision Contrast Test System (VCTS 6500 e 6000) (Vistech, Dayton, OH), Contrast Sensitivity Vision (CSV 1000 E) (Vector Vision, Greenville, OH), Functional Acuity Contrast Test (F.A.C.T) (Vision Science Research Corporation, Walnut Creek, California) and Ohio contrast cards. The most commonly used CS charts for typically developing paediatric population and those used in children with special needs are described below and their basic specifications and repeatability indices are summarized in tables 2.5 and 2.6)

Functional acuity contrast test (F.A.C.T)

The original functional acuity contrast test (F.A.C.T) (Functional Acuity Contrast Test F.A.C.T.)) was developed by Arthur P. Ginsburg in 1983. The new version is an improvisation of the older version. The F.A.C.T (figure 2.18) measures patient's vision with various spatial frequencies and contrast, thus simulating a real-world scenario. The test assesses the complete CS function from the lowest to highest spatial frequencies. It uses sinusoidal gratings of five spatial frequencies and nine different contrast levels for each spatial frequency. The contrast level between each spatial frequency is 0.15 log units (Functional Acuity Contrast Test F.A.C.T.). The spatial frequencies included in FACT are 1.5 CPD, 3 CPD, 6 CPD, 12 CPD and 18 CPD. The log contrast sensitivity (logCS) covered at each spatial frequency level is as follows: 1.5 CPD (0.85-2.00 logCS), 3 CPD (1.00-2.20 logCS), 6 CPD (1.08-2.26 logCS), 12 CPD (0.90-2.08 logCS) and 18 CPD (0.60-1.81 logCS) (Buhren et al., 2006). The grating

patch size is 1.7 degrees and each patch is either tilted +15˚, 0˚ and -15˚ (Functional Acuity Contrast Test F.A.C.T.).

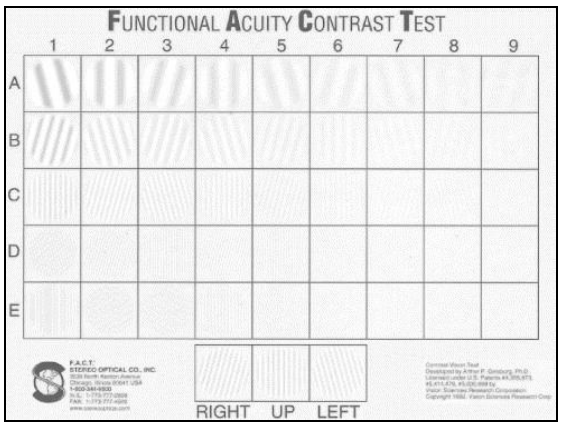


Figure 2.18: Functional acuity contrast test
(Source: www.stereooptical.com)

Hiding Heidi low contrast face test (HH cards)

Hiding Heidi low contrast face test (figure 2.19) (Hiding Heidi Low Contrast Face Test (from Good-lite)) is developed by Lea Hyvarinen. It uses picture contrast to assess the low contrast information in preverbal/non-verbal children and in those with special needs. This 'face test' follows the two-alternate forced choice technique. The test consists of a total of 3 cards having 6 different contrast levels (printed on both sides) and one blank card. The contrast levels include 100%, 25%, 10%, 5%, 2.5% and 1.25%. The cards are about 23 cm x 23 cm with a face diameter of 17 cm. The outer band of the circle is approximately 8 mm (3 CPD) wide. The lines that form the hair and the mouth of 'Heidi' are approximately 4 mm (1.5 CPD) wide. The band width of the outer circle of the eye is approximately 2 mm (0.75 CPD) and the diameter of the centre eyeball is approximately 25 mm (9 CPD) (Chen & Mohamed, 2003). The examiner presents a blank card and one contrast card to assess the child's response at a recommended distance of 50 cms. The contrast cards are presented in descending order of limits and if the child is unable to appreciate the specific contrast card, the examiner presents the next easily appreciable card and 2 out of 3 correct responses is considered as the stopping criteria. Both the blank and contrast card are moved at the same speed horizontally. However, vertical movement of cards should be considered in children with horizontal nystagmus (Hiding Heidi Low Contrast Face Test (from Good-lite)).

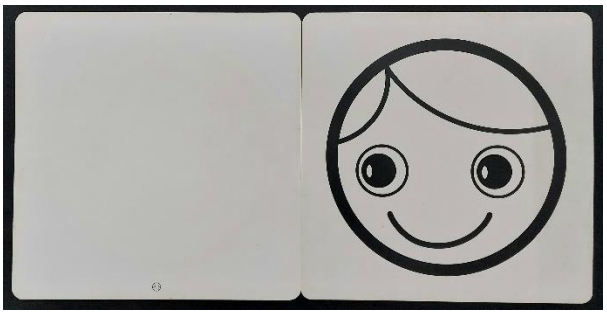


Figure 2.19: Hiding Heidi low contrast face test

Ohio contrast cards

The Ohio contrast cards (figure 2.20) were developed by Brown et al (Hopkins et al., 2017). The clinical utility of these cards was first tested in a visually impaired cohort by Hopkins et al in 2017 (Hopkins et al., 2017). The gratings are horizontally oriented and are presented to the child at a distance of 50 cms. The examiner looks through the central peep-hole to judge the child's responses. The contrast cards have square-wave gratings at a very low spatial frequency of 0.15 cycles per degree and the contrast threshold varies from 2.2% to 100%. The findings from Ohio contrast cards were found to correlate significantly to the children's quality of life when carried out on a cohort of children with special needs (Hopkins et al., 2017). These cards were noted to be 0.9 $\log_{10}$units (Michelson) more sensitive than Pelli-Robson CS chart (i.e., 3 lines on the Pelli-Robson chart) when tested on 7-20 years old students with vision impairment (Osman et al., 2021).

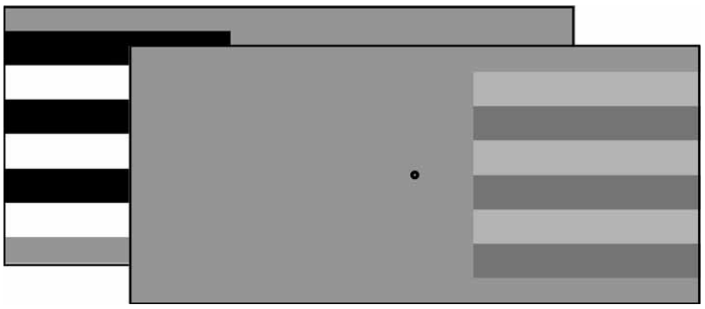
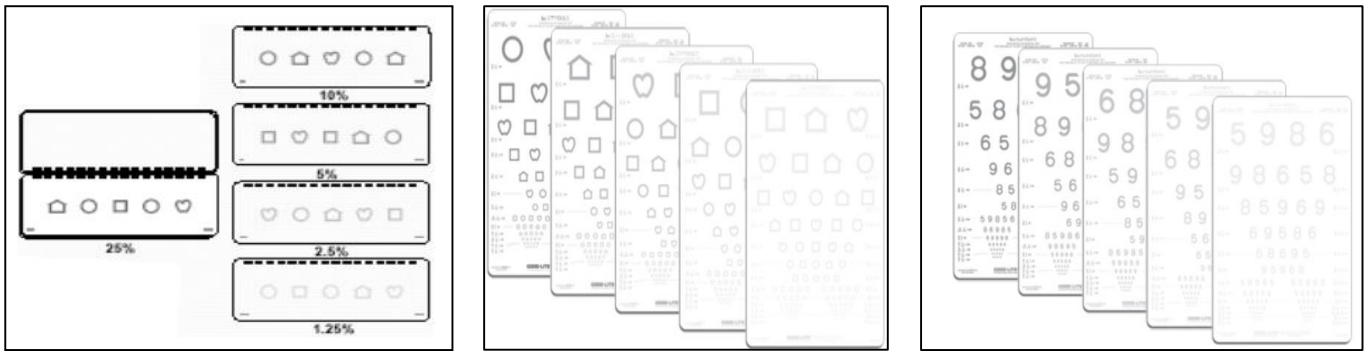


Figure 2.20: Ohio contrast cards
(Source: Hopkins et al, 2017)

LEA low contrast tests

The LEA low contrast tests are available as follows: flip chart (figure 2.21a) with fixed size of 10M corresponds to a visual acuity of 1.0 logMAR (20/200) at the most common testing distance of 1 meter in the flip chart. Also, as conventional charts with varying stimuli size in 5 different contrast levels: 1.25%, 2.5%, 5%, 10% and 25% (LEA SYMBOLS® Low Contrast Test)) (figure 2.21b). Both the tests

include optotypes that are similar to the high contrast LEA symbols. The four symbols of an apple, ball, square and house are used in this test. The conventional testing distance of 3 metres is used and the chart can also be moved closer if needed, however, recoding the appropriate distance is important to report the outcome. At least three out of five optotypes should be correctly identified to consider that particular contrast level (LEA contrast sensivity test (from Good-lite)). The other stimuli in the contrast charts from LEA testing tools include the LEA numbers (figure 2.21c).



(a) (b) (c)

Figure 2.21: LEA low contrast tests: (a) LEA low contrast flip chart,
(b) LEA symbols low contrast acuity test (c) LEA numbers low contrast acuity test
(Source: Good-lite(LEA contrast sensivity test (from Good-lite))

Mayer-Kran Double-Happy low contrast test

Mayer-Kran Double-Happy low contrast test (figure 2.22) was recently developed by Luisa Mayer and Barry Kran (Mayer et al., 2020). (Mayer-Kran Double-Happy low contrast test (from Precision Vision)) This test was developed primarily for children who cannot be tested using standard letter optotypes. The stimulus consists of a smiling schematic face which is offset from the centre of the card. As the face is identical when the card is rotated by 180 degrees, it is called as the double-happy test. The test is available under 2 sets: (i) screening test consists of 6 cards in the following contrast levels: 89%, 36%, 25%, 12.6%, 6.3%, 3.2% and 2.2%. (ii) full set consists of 16 cards including the blank card. The contrast levels are more finer: 89%, 71%, 50%, 36%, 25%, 17.8%, 8.9%, 6.3%, 4.5%, 3.2%, 2.2%, 1.6%, 1.1%, 0.8% (Mayer-Kran Double-Happy low contrast test (from Precision Vision)).

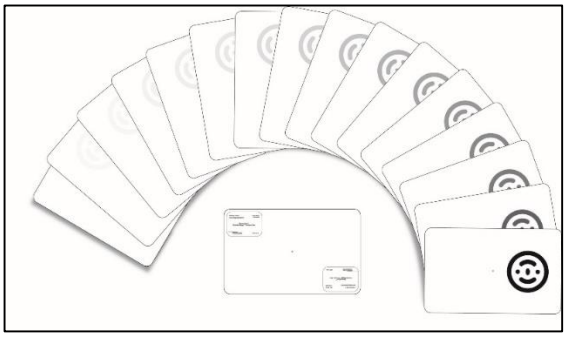


Figure 2.22: Mayer-Kran Double-Happy low contrast test
(Source: (Mayer-Kran Double-Happy low contrast test (from Precision Vision))

Pelli-Robson contrast sensitivity test

The Pelli-Robson contrast sensitivity test (figure 2.23) (Pelli-Robson Contrast Sensitivity Chart (from Precision Vision)) is a well-established and widely used chart to measure CS (Pelli et al., 1988). It uses Sloan letters, arranged in 16 groups of 3 letters. The letters are of 20/630 size and subtend 1 cycle per degree at the recommended distance of 1 metre. Each triplet corresponds to 0.15 log unit and the triplet is considered as the correct response if atleast 2 out of 3 letters are read appropriately. The contrast threshold that can be tested using the Pelli-Robson chart ranges from 100% to 0.56% (Richman et al., 2013). The normative CS for younger adults with a mean age of 22.5 ± 4.3 years was found to be 1.80 log units or above, whereas for the older adults with a mean age of 70.2±6.7 years it was 1.65 log units. The repeatability of the CS scores was noted to be within ±0.15 log units or ±1 step. Hence, a score of 0.30 log units change is considered to be significant (Elliott et al., 1990). Pelli-Robson chart has been used among normally sighted children aged 6 to 12 years of age and the mean CS thresholds was found to range between 1.63±0.12 and 1.65±0.06 log CS in the right eye and 1.72±0.08 and 1.76±0.07 log CS in the left eye (Leat & Wegmann, 2004) (Mantyjarvi & Laitinen, 2001).

Figure 2.23: Pelli-Robson contrast sensitivity chart
(Source: www.precision-vision.com)

Mars letter contrast sensitivity test

The Mars letter contrast sensitivity test (figure 2.24) was earlier known as the Lighthouse letter CS test. This test uses letters to test the peak visual CS by assessing processing of relatively low retinal spatial frequencies. The chart is printed on rigid plastic and has dimensions of 23x35.5 cms (Dougherty et al., 2005). The chart consists of 48 Sloan letters having 6 letters arranged across 8 rows. Each letter subtends 2 degrees at 50 cms testing distance. The letters are to be read left to right and the contrast of the letters decreases by a constant factor of 0.04 log unit. The log CS varies from 0.04 log CS to 1.92 log CS. The chart needs to be illuminated uniformly having an ideal luminance in the chart's white background of 85 cd/m^2. It is suggested that the luminance should be at least 60 and less than 120 cd/m2 in all white areas of the chart. An illuminance range of 189 to 377 lux is suggested, with an optimum of 267 lux. The chart is designed for carrying out the test at a distance of 50 cms but can be used within the range of 40 cms to 59 cms, which is the habitual near working distance (Arditi, 2005). The letter optotype is approximately equivalent to 20/480 at a distance of 50 cms. Appropriate near correction should be placed during the test, or else a complete distance correction with an addition of +2.00D. If the individual has poor visual acuity, an addition of +4.00D is used and the testing distance is reduced to 25 cms. The final contrast of the letter that is read by the individual before which s/he gives incorrect responses for two consecutive letters is noted. This value along with a correction for earlier wrong responses, gives the final log CS of the individual (User Manual: The Mars Letter Contrast Sensitivity Test; Mars Perceptrix, 2013). The Mars letter contrast sensitivity test was found to have good agreement with the Pelli-Robson contrast sensitivity test (95% limits of agreement (LoA): ± 0.21 log units) for adults. Both charts were also found to have similar repeatability measures (95% LoA: ± 0.20 log units) when tested on adults with vision impairment and those who were normally sighted (Dougherty et al., 2005).

Figure 2.24: Mars letter contrast sensitivity test

(Source: www.marsperceptrix.com)

Bailey-Lovie low contrast acuity test

The Bailey-Lovie low contrast acuity test measures the low contrast acuity at a fixed contrast level of 10% Michelson's contrast (Bailey-Lovie chart set (from Precision Vision)) . This chart has fixed contrast level throughout the chart with varying sizes of the optotypes. The high and low contrast charts from Bailey-Lovie (figure 2.25) are printed one behind the other, such that it is easy for clinical use. It is often considered that 2 lines or more difference between the high and low contrast acuities indicates a significant difference and is suggestible of impaired CS (Brown & Lovie-Kitchin, 1989). This easy-to-understand interpretation of the low contrast acuity values obtained using the chart could be one of the reasons for its popularity in low vision clinics, especially in the low vision care units. The low contrast acuity that can be measured on the Bailey-Lovie low contrast chart ranges from 20/253 to 20/12.6 and each letter corresponds to 0.02 logMAR. The chart needs external illumination and the chart illuminance is recommended to be of 480 lux (Institution, 1968). The chart is calibrated for a distance of 6 metres; however, the distance can be varied as per convenience with the caution of considering the correction factor for the final outcome. The chart dimensions are approximately 53x60 cms. The optotypes include ten British standard 5×4 non-seriffed letters. The chart follows a uniform logarithmic progression throughout the chart, similar to the high contrast test (Bailey-Lovie chart set (from Precision Vision)) .

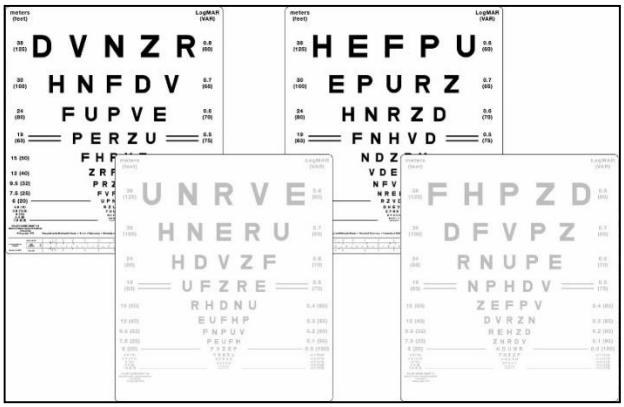


Figure 2.25: Bailey-Lovie high and low contrast acuity charts
(Source: www.precision-vision.com)

SpotChecks contrast sensitivity test

The SpotChecks contrast sensitivity test (figure 2.26), an improvised version of CamBlobs™ was designed by John Robson (available from Precision Vision(SpotChecks (from Precision Vision)). The test was designed for self-monitoring, home testing purpose and is an inexpensive alternative. Unstandardized distance can be used for testing purposes. The worksheet has 5 columns and 24 rows of

spots with decreasing contrast from top to bottom. Across the row the CS decreases by 0.01 logCS from left to right. The size of the spot is 9 mm in diameter and at a distance of 40 cms subtends ~1.3° at the eye. The range of CS measured includes: 0.9 to 2.09 logCS at a step-size of 0.05 logCS.

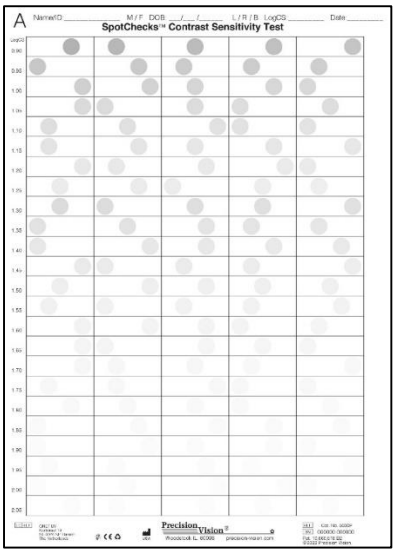


Figure 2.26: SpotChecks contrast sensitivity test
Source: Precision Vision (SpotChecks (from Precision Vision))

Test name	**Type of stimuli/optotypes**	**Contrast sensitivity range**	**Recommended test distances**
Functional acuity contrast test	Sinusoidal gratings	1.5 CPD (0.85-2.0 logCS) 3 CPD (1.0-2.2 logCS) 6 CPD (1.08-2.26 logCS) 12 CPD (0.9-2.08 logCS) 18 CPD (0.6-1.81 logCS)	46 cms
Ohio contrast cards	Square-wave gratings	0.0 to 1.66 logCS	57 cms
Hiding Heidi cards	Heidi's face	0.0 to 1.9 logCS	50 cms *(distance can be varied, but should be documented)*
LEA low contrast tests *Flip chart* *Low contrast acuity test*	Symbols: Apple, ball, square and house Symbols/numbers	25%, 10%, 5%, 2.5% and 1.2% contrast threshold	3 metres *(distance can be varied, but should be documented)*
Mayer-Kran Double-Happy low contrast test	Happy face	0.05 to 2.1 logCS	40 cms
Pelli-Robson contrast sensitivity test	Sloan letters	0.0 to 2.25 logCS	1 metre
Mars letter contrast sensitivity test	Sloan letters	0.04 to 1.92 logCS	50 cms
Bailey-Lovie low contrast acuity test	Non-seriff letters	20/253 to 20/12.6 *(fixed contrast level:10%)*	3 metres
SpotChecks contrast sensitivity test	Spots	0.9 to 2.09 logCS	No standardized test distance

Table 2.5: Summary of the basic specifications of commonly used contrast sensitivity tests

Test name	Study	Cohort	Age range	CS ranges obtained	Testability rate	Testing time	Repeatability	Remarks
Hiding Heidi low contrast face test	Leat et al (Leat & Wegmann, 2004)	88 normally sighted children	1 - <8 years	Median: 1.9 logCS	100%	-	-	There was a ceiling effect among all age groups. Significantly different values when compared with Pelli-Robson chart 95% LoA with Pelli-Robson: -0.54 to 0.14 logCS
	Chen and Mohamed (Chen & Mohamed, 2003)	30 university students	20-25 years	1.77±0.22 logCS	100%	-	95% LoA: -0.12 to 0.16 logCS, r=0.95	95% LoA with FACT: -0.55 to 0.17 logCS (across 3 different spatial frequencies)
Ohio contrast cards*	Hopkins et al (Hopkins et al., 2017)	26 individuals with VI	10-20 years	0.19 log $_{10}$ units below the maximum possible CS predicted by the model using TAC-II and letter CS tests	96.15%	64±37 sec	-	Values obtained using Ohio contrast cards were independently and statistically significantly correlated with quality of life
	Osman et al(Osman et al., 2021)	30 school-aged children with VI	7-20 years old	-	90%	-	Mean test-retest difference: -0.07±0.21, 95% LoA: ±0.42	Equally repeatable when compared to Pelli-Robson chart

Test name	Study	Cohort	Age range	CS ranges obtained	Testability rate	Testing time	Repeatability	Remarks
LEA low contrast tests	Leat et al (Leat & Wegmann, 2004)	67 normally sighted children *(done at 28 cms and at 1m)*	2.5 - <8 years	Median: 2.22 logCS, when recalibrated was 1.65 logCS	100%	-	-	LEA symbols at 28 cms after recalibration had best agreement with Pelli-Robson chart
	Little et al (Little et al., 2013)	45 children with cerebral palsy, 44 children with Down syndrome, 211 controls	4-18 years	Mean low contrast acuities: Cerebral palsy = 0.50 ± 0.2 logMAR, Down syndrome = 0.73 ± 0.2 logMAR, controls = 0.37 ± 0.1 logMAR	Cerebral palsy: 66%, Down syndrome: 59%	~ 4-6 min for each participant for both high and low contrast acuity testing	- -	The mean difference between high and 2.5% low contrast acuities for controls was 0.4 logMAR (95% LoA: ±0.22 logMAR)
Mayer-Kran Double-Happy low contrast test	Mayer et al (Mayer et al., 2020)	23 children with ocular VI, 20 with CVI	2-18 years	B/O: 0.05 to 0.21 logCS	100%	2-3 min for total testing	Inter-examiner variability was not statistically significant (mean=-0.003±0.22 logCS; p=0.46), ICC: 0.921	Values obtained using Double-Happy test was marginally better predictor of diagnosis than visual acuity

Test name	Study	Cohort	Age range	CS ranges obtained	Testability rate	Testing time	Repeatability	Remarks
Pelli-Robson contrast sensitivity test	Leat et al (Leat & Wegmann, 2004)	17 normally sighted children	6 - <8 years	Median: 1.68 logCS, 95th percentile: 1.58 logCS	100%	-	-	Significant difference in the CS obtained using Pelli-Robson chart for children vs. adults ($p<0.0001$)
		15 normally sighted adults	23-27 years	Median: 1.79 logCS, 95th percentile: 1.59 logCS	100%	-	-	
	Anderson et al (Anderson et al., 2023)	43 normally sighted children	4-12 years	4-5 years: 1.86±0.08 logCS 6-7 years: 1.95±0.07 logCS 8-10 years: 1.92±0.06 logCS 11-12 years: 1.99±0.08 logCS	-	-	-	Statistically significant increase in the logCS was associated with age (0.01 logCS/year and $p=0.02$)
	Osman et al (Osman et al., 2021)	30 school-aged children with VI	7-20 years old	-	90%	-	Mean test-retest difference: -0.07±0.21, 95% LoA: ±0.42	Equally repeatable when compared to Ohio contrast cards
Mars letter contrast sensitivity test^	Dougherty et al (Dougherty et al., 2005)	20 normally sighted young adults 17 normally sighted older adults 17 adults with low vision	22-86 years	Young adults: 1.72±0.06 logCS Older adults: 1.76±0.05 logCS Low vision adults: 1.27±0.41 logCS	-	-	Intra-observer repeatability: 95% LoA = +/-0.20 log CS	Excellent agreement with the Pelli-Robson test (95% LoA of +/- 0.21 log CS) for all subjects

Test name	Study	Cohort	Age range	CS ranges obtained	Testability rate	Testing time	Repeatability	Remarks
Mars letter contrast sensitivity test^	Thayaparan et al (Thayaparan et al., 2007)	12 normally sighted adults 41 adult ophthalmology patients	> 18 years	-	-	-	Intra-observer repeatability: CR: 0.121 logCS	LoA with Pelli–Robson chart was- 0.29 to 0.15 logCS
Bailey-Lovie low contrast acuity test[#]	Brown and Lovie-Kitchin (Brown & Lovie-Kitchin, 1989)	86 normally sighted individuals	14-74 years	1.48 to -0.02 logMAR (mean difference of 0.26 logMAR between the high and the low contrast acuity)	-	-	-	Correlation of peak contrast sensitivity function with low contrast acuity: r:0.897
SpotChecks Contrast sensitivity test	Anderson et al(Anderson et al., 2023)	43 normally sighted children	4-12 years	4-5 years: 1.84±0.08 logCS 6-7 years: 1.91±0.1 logCS 8-10 years: 1.98±0.07 logCS 11-12 years: 2.02±0.04 logCS	-	3-15 min	Mean difference in test-retest: 0.01 logCS, CR: 0.14 logCS (95% LoA: -0.13 to 0.14 logCS)	Good agreement with Pelli-Robson test (mean difference was 0.00 logCS (95% LoA: −0.19 to 0.2 logCS). Statistically significant increase in logCS was associated with age (0.02 logCS/year, p <0.001)

Table 2.6: Clinical utility indices of currently available contrast sensitivity tests used in children collated from different studies

*(*will be made available soon (personal communication with the developer, ^[#]as studies were not available in children, the description is given for adult-based studies (CS=contrast sensitivity, r=correlation coefficient, LoA: limits of agreement, ICC: intra-class correlation)*

Key learnings

- 5/9 preferential looking acuity tests *(TAC-II, LEA gratings paddle, Keeler acuity cards, Cardiff acuity cards and Peekaboo Vision app)* report repeatability indices in the SEN cohort.
- Teller acuity cards-II are the most extensively used grating acuity test
- 3/8 contrast sensitivity tests *(Pelli-Robson contrast sensitivity test, Ohio contrast cards and Mayer-Kran double happy test)* report repeatability indices in the SEN cohort

Chapter 3 : Introduction to the study

3.1 Chapter overview

In the previous chapters, definitions, terminologies, prevalence of SEN and CVI, a detailed understanding of CVI and the most commonly used tools of VA and CS as part of paediatric eye care have been discussed. With this background of literature, we will move into the introduction to the current study in this chapter. Study rationale and research question, defining the study objectives, study hypotheses, basic overview of the research design and framework used in the current study and importance of the study will be discussed as part of this chapter.

3.2 Study rationale and research question

Children with CVI are likely to have moderate to severe vision impairment (Mercuri et al., 1999) and the importance of identifying this condition at the earliest possible opportunity and referring for early intervention services is the key to rehabilitation in all sensory areas (Philip & Dutton, 2014). Functional visual assessment (for example tracking an illuminated/non-illuminated objects of a particular size, (see section 1.5.8) may be useful in understanding the visual capabilities of children with SEN (Dale et al., 2017), but may not be easily translated into the visual functions that are tested on a regular basis in the eye clinics. Vision stimulation therapy is carried out particularly in young children on the basis of making the most of the critical period, i.e., from birth to ~6 to 8 years of age, to allow children to maximize their visual potential and avoid long-term consequences such as amblyopia (Gunton, 2013). However, there is very little evidence of the effectiveness of early visual intervention in terms of rehabilitation therapies (Alimovic et al., 2014). Some studies report an improvement in visual functions, functional vision and vision skills post vision stimulation therapy in a small minority of studies (Hoyt, 2003; Malkowicz et al., 2006; Tsai et al., 2016), but high quality studies with more objective outcome measures are still needed to establish the evidence (Delay et al., 2023). The most commonly tested visual function in the clinic, i.e., VA and the visual function that correlates better to functional vision, (Zimmerman et al., 2011) i.e., CS are assessed as part of this study. Although VA and CS are used as outcome measures in a couple of studies (Alimovic et al., 2014; Alimovic & Mejaski-Bosnjak, 2011), the validation of the tool being used is important to appropriately interpret the findings *(validation measures that will be used in this study are mentioned in section 3.5).*

As CVI is reported to be a leading cause amongst children with SEN in developing countries (Pehere et al., 2018) and in the developed world as well (Alagaratnam et al., 2002; Ozturk et al., 2016; Rogers, 1996), we aim to validate VA and CS tools, as this step will help in determining suitable tests among

existing ones for this cohort. Testing the repeatability of these clinical tools is also essential in children with CVI due to the variable responses that may result from their frequency of seizures, effect of antiepileptic medications, severity of brain damage and poor developmental milestones. Therefore, such factors also need to be captured for understanding the outcome measures of VA and CS appropriately, such as development quotient/age, frequency of seizures, brain imaging findings and functional vision measure. Understanding demographics of these children is also very helpful for early diagnosis, and to facilitate referral pathways. Therefore, with this rationale, we established the study objectives that are given below.

3.3 Study objectives

1. To describe the demographic and clinical characteristics of children with CVI and age-similar typically developing children.

2. To determine the limits of agreement between two tests of grating VA, i.e. Teller acuity cards-II (Mash & Dobson, 1998) and Peekaboo Vision app (described in section 2.2.1) (Livingstone et al., 2019) in children with CVI and compare with age-similar typically developing children.

3. To determine the limits of agreement between two tests of CS, i.e. Ohio contrast cards (Hopkins et al., 2017) and Hiding Heidi cards in children with CVI and compare with age-similar typically developing children.

4. To determine the intra-observer test-retest repeatability of two different VA (Teller acuity cards-II and Peekaboo Vision app) and CS (Ohio contrast cards and Hiding Heidi cards) tests in children with CVI and in age-similar typically developing children.

5. To determine the association of the visual functions with developmental quotient, seizure history and activity, brain imaging findings and functional vision measure in children with CVI.

3.4. Study hypotheses

Null hypotheses

1. In children with CVI, the tests of VA and CS will have similar clinical utility indices, agreement and repeatability indices as that of age-similar typically developing children.

2. Factors such as seizure frequency, developmental age, extent and location of brain damage and functional vision will not have any effect on VA and CS in children with CVI.

Alternate hypotheses

1. In children with CVI, the tests of VA and CS will not have similar clinical utility indices, agreement and repeatability indices as that of age-similar typically developing children.

2. Factors such as seizure frequency, developmental age, extent and location of brain damage and functional vision will have an effect on VA and CS in children with CVI.

3.5 What is validation?

Validation of a tool involves objective evidence of reproducibility and accuracy (Walton, 2001). Reproducibility, not only within itself, but with any gold-standard that exists. Gold-standard in medicine and statistics, essentially refers to *"a diagnostic test or benchmark that is the best available under reasonable conditions."* Agreement and test-retest repeatability have primarily been used as part of the validation process in several clinical studies in vision sciences (Leat & Wegmann, 2004; Livingstone et al., 2019; Lovie-Kitchin, 1988; Preston et al., 1987). In the current study, VA and CS tests were validated by determining their clinical utility indices[7], agreement between the test measures and intra-observer test-retest repeatability. We were unable to report inter-observer repeatability indices and we discuss the reasons for this as part of the study limitations (see section 8.2).

3.6 Research design and framework

A prospective case-control study was undertaken on children with CVI presenting for neurology consultation at Rainbow Children's hospitals, Hyderabad, India. An informal audit of medical records of children with CVI presenting to the Special Needs Vision Clinic at LVPEI, Hyderabad, India (see section 4.2) revealed that the chief complaints as reported by parents included lack of eye contact, difficulty with facial recognition and watching TV. Considering the primary concerns of parents, the visual functions that are closely associated and highlighted include VA and CS parameters. Clinicians are more familiar with testing of these two visual functions and several assessment tools have also been developed for both adults and children. As a result, these two parameters were prioritized to be studied as part of this research. For each parameter, two different tests were chosen from the most

[7] *Clinical utility can be defined in terms of testability, testing time, comparison with other testing tools, range of acuity that can be measured and ease of using the tool.*

commonly used tests in the paediatric population by reviewing appropriate literature and with an intent to explore child-friendly app-based tests. Since data can be highly variable from this cohort, repeatability is essential. Therefore, repeatability was also carried out as part of this study. The inter-examiner repeatability measure was carried out using video analysis, as there was an increased likelihood of the child becoming fatigued and restless if a second observer performed the same set of tests. The other important details that were recorded to study the association included: MRI findings/grading, developmental quotient, severity of CVI, birth history, association of seizures and medication if any. A control group consisting of chronological age-matched typically developing children were also recruited to compare the repeatability indices of the tests of visual functions.

3.7 Importance of the study

Children with CVI can have a spectrum of visual functioning, ranging from low to high (Pehere & Jacob, 2019). Previous studies have largely focused on the high functioning CVI group (Chandna et al., 2021; Chokron et al., 2021; Manley et al., 2022). Visual functions of high functioning children with CVI are easier to ascertain when compared to the low functioning group using conventional visual function tools, because of normal to near-normal VA and concerns primarily with higher order visual processing (Chandna et al., 2021). Given that a larger proportion of children with CVI present in the low to moderate functioning categories in the investigating centres (based on the PI's clinical experience) and also given the Indian context (Pehere & Jacob, 2019), it is important to validate clinical tools of visual functions in these cohorts, from whom eliciting responses may not only be challenging but also variable due to several factors such as seizures and developmental delay.

The five study objectives have important clinical implications in the assessment and management of children with CVI.

Demographic and clinical characteristics of CVI

Several factors can contribute to the occurrence and severity of CVI. Cerebral visual impairment still largely remains as the diagnosis of exclusion (McConnell et al., 2021), this is likely to have an impact on the cross-referral system which can in turn delay the appropriate service that needs to be offered to the child. Although several studies describe the demographic and clinical characteristics of children with CVI (Fazzi et al., 2007; Pehere et al., 2018; Philip & Dutton, 2014), it is very crucial to understand these factors pertinent to the cohort being studied for better understanding and

interpretation of the vision-related parameters (such as the visual functions, functional vision, validating the visual function tools) better, which is the primary focus of the study.

Validation of tests of VA and CS

Determining validated tools for children with CVI will be important as the clinical assessment for these children could be standardized for commonly measured visual functions. Visual acuity has remained the most commonly reported outcome measure in several studies across different types of intervention (Cotter et al., 2006; Fazzi et al., 2021; Matsuba & Jan, 2006). However, intervention studies in children with CVI do not have standardized and uniform outcome parameters, primarily due to the lack of validated clinical tools in the cohort (Delay et al., 2023). In addition to acuity measures, clinical validation (see section 3.5) of a tool *(for e.g., in this case PV app)* includes comparison with the gold-standard *(for e.g., in this case the most commonly used paediatric grating acuity test TAC-II)* on several parameters such as the testability, testing duration, acuity range that is testable, child's engagement during the test procedure and the tool's agreement with the gold-standard and repeatability indices.

Several activities of daily living are likely to be negatively impacted through impaired CS (Philip & Dutton, 2014; West et al., 2002) and this parameter remains a useful test to be included when designing a protocol of appropriate clinical tests. In the current study, OCC is compared to the HH cards *(considered as the gold-standard, i.e., most commonly used paediatric CS tool)* and this will help us determine the most appropriate tool for CS assessment children with CVI.

The results of the current study will be helpful in choosing tests of visual function to quantify the effectiveness of any intervention (such as: rehabilitative, optical, surgical, and medical). Additionally, the use of validated clinical tools helps in understanding the vision developmental pattern in this cohort of children. Once validated, if applicable, the clinical tools can be used for examining children with CVI and may prove useful in other cohorts of children with SEN such as in children with global developmental delays, cerebral palsies, DS, attention deficit hyperactive disorders and other developmental delays. In the vision rehabilitation area, these tools can also be used to objectively quantify effectiveness of vision stimulation therapies, changes with developing age, impact of medication (for example: seizure medications) in children having vision impairment due to neurological conditions, particularly during the critical window of visual development, i.e. from birth to ~ 6 to 8 years of age (Gunton, 2013).

Visual functions and associative factors

As children with CVI are likely to have developmental delays in multiple areas, it is important to study and interpret how VA and CS results might relate to factors such as chronological and developmental age, functional vision, seizure frequency, refractive errors and neuroimaging findings. This is useful for better understanding of visual functions in children with CVI.

Chapter 4 : Preliminary studies on children with special educational needs

4.1 Chapter overview

In chapter 2, we discussed currently available VA and CS tests commonly used in the SEN population and typically developing children. Children with CVI fall under the large umbrella of SEN cohort and will need assessment beyond VA and CS as discussed in section 2.4. The 3 preliminary studies that were carried out by the PI to set the scene for the main doctoral work are discussed in this chapter. Study 1 provides a rationale for choosing only VA and CS for testing children with CVI for the purposes of this study. Study 2 and 3 describe the feasibility and determines clinical utility of a Peekaboo Vision app (study 2) and OKKO Health app (study 3) against the conventional card-based 'gold-standard' TAC-II in a representative cohort of children with SEN, i.e., Down syndrome (DS).

4.2 Preliminary study: 1: Parent-reported visual concerns in children with special educational needs[8]

Introduction

Children with SEN are likely to have issues with speech and therefore may find it difficult to verbally communicate their concerns (Garfin & Lord, 1986; Pennington et al., 2020). Clinicians commonly rely on the parents/caregivers to report the child's visual concerns. Several studies have established that children with SEN have visual challenges due to the higher prevalence of ocular conditions, such as refractive errors, strabismus, accommodative disorders compared to their typically developing counterparts (Black, 1982; Das et al., 2010; Roizen et al., 1994). As part of the vision assessment, testing all the visual functions could be difficult due to the limited attention span typically noted in this cohort (Gogri et al., 2015). Hence obtaining maximum clinical information with minimal chair-time is the key for successful clinical assessment. In this study, we aimed to determine the common reasons that prompted the parents/caregivers to bring their child(ren) to consult at a tertiary eye care unit for the first time and associate them with the visual functions.

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[8] This preliminary study was presented at the British Congress of Optometry and Vision Sciences 2020 conference as a scientific poster, held virtually in September 2020 and the poster is given in the appendix A2.

Methodology

A retrospective review of medical records of children (<18 years) attending the Special Needs Vision Clinic for the first time at a tertiary eye care unit in South India during the months of April and May 2019 was carried out to determine the chief purpose of their visit. Demographic details were also noted.

Results

Fifty-one medical records of children (males, n=31, 61%) with a mean age of 10.05±6.1 years were reviewed. The three most common ocular conditions noted were optic atrophy (n=21, 41.1%), refractive errors (n=8, 15.6%) and retinal pathologies (n=7, 13.7%). The three most common causes of delay were developmental delay (n= 32, 62.7%), DS (n=5, 9.8%) and Attention Deficit Hyperactive Disorder (n=3, 5.8%). (table 4.1)

Diagnoses	**n (%)**
Ocular	
Optic atrophy	16 (31.3)
Cerebral visual impairment	9 (17.6)
Refractive errors	9 (17.6)
Retinal pathologies	8 (15.6)
Strabismus	6 (11.7)
Lenticular abnormalities	3 (5.8)
Special educational needs	
Developmental delay	34 (66.6)
Down syndrome	5 (9.8)
Attention deficit hyperactive disorder	3 (5.8)
Cerebral palsy	2 (3.9)
Others (hypothyroidism, Laurence-Moon-Bardet-Biedl syndrome)	7 (13.7)

Table 4.1: Ocular diagnoses and causes of special needs in children attending a Special Needs Vision Clinic in India
(primary ocular diagnosis has been mentioned)

The main purposes of the visit as reported by the parents/caregivers included: general vision check-up with no specific visual complaints as the child has delay in other areas (n=15, 29.4%),

maintaining eye contact (n=12, 23.5%), recognizing faces (n=12, 23.5%) and bumping into objects (n=7, 13.7%). (figure 4.1)

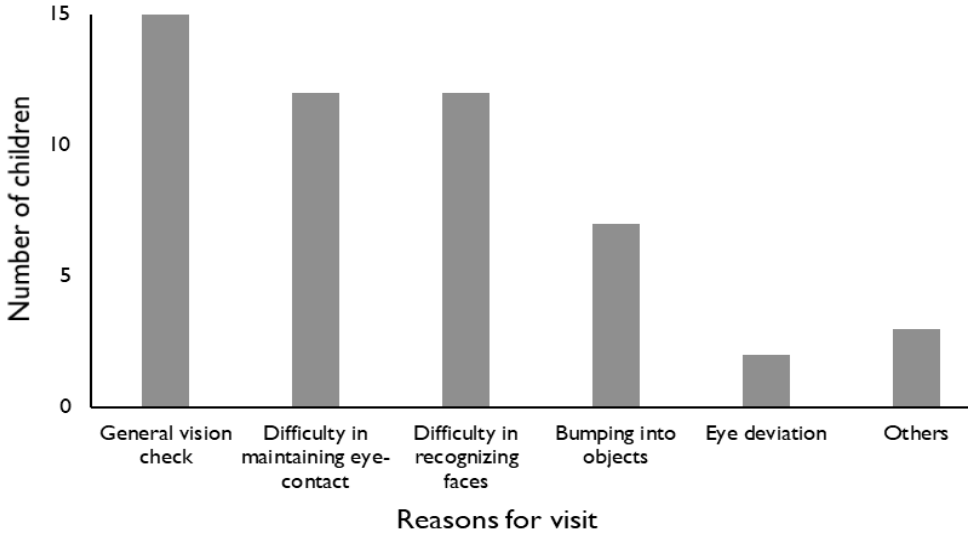


Figure 4.1: Reasons for consulting at the Special Needs Vision Clinic in India
(others included copying from board and eye shaking)

The associated visual functions for these most commonly reported reasons to visit were VA (distance and near), CS and peripheral visual fields. (table 4.2)

Reasons	Associated visual functions/tests
Difficulty in maintaining eye-contact	Refractive error assessment Contrast sensitivity Binocular vision status Visual acuity Visual fields
Difficulty in recognizing faces	Visual acuity Contrast sensitivity Refractive error assessment Binocular vision status
Bumping into objects	Visual fields Contrast sensitivity Binocular vision status
Eye deviation	Binocular vision status Refractive error assessment Visual acuity

Table 4.2: Most commonly reported visual concerns and their associated visual functions/tests

Discussion and conclusions

Through this pilot study, we ascertained the most common reasons that prompted parents/caregivers to bring their child(ren) to a tertiary eye care unit. By paying attention to their chief concerns, clinicians will be able to prioritize the visual functions that need to be tested. This will also be helpful to plan clinical protocols for interventional studies in children with SEN. Based on this pilot data, the visual functions that emerge as the most affected due to the neurological conditions include VA, CS and peripheral visual fields.

Key findings

- The most commonly reported visual concerns reported by parents were difficulty in maintaining eye contact and recognizing faces
- The associated visual functions for the most commonly reported concerns were VA (distance and near), CS and peripheral visual fields

4.3 Preliminary study 2: Clinical utility of "Peekaboo Vision" application for measuring grating acuity in children with Down syndrome

Introduction

While the heterogeneity in children with special educational needs (SEN) can be wide in terms of the causes, types and severity of the disability, similarities are likely to be present as well. In the study by Wilton et al (Wilton et al., 2021) on behavioural features of both the cohorts, children with Down syndrome (DS) were more likely to experience concerns with visual perceptual skills similar to those children with CVI, for e.g. difficulty/slow in copying words/drawings, difficulty in walking on uneven ground and difficulty in seeing something which is pointed out at a distance. These 3 specific concerns which are commonly present in children with CVI, were noted to be present in more than 50% of children with DS in this study. However, the authors conclude by stating that further research is warranted to determine the aetiology of visual perceptual problems in children with DS. Considering the above mentioned similarities, this feasibility study was considered useful for the PI to get familiarized with using the clinical tools in a specific group of special needs cohort. Notable differences also exist such as children with DS not being limited by their eye-hand coordination skills and exhibiting fewer behavioural problems when compared to children with other developmental disabilities (Eisenhower et al., 2005).

The feasibility study was carried out on children with DS to understand the practical concerns that the principal investigator (PI) was likely to face during the main study. There was an opportunity for organizing a vision screening camp for this specific group of children during the period when study protocols were being finalized for the main study. Therefore this was considered as a convenience sample to help refine the main study methodology. Also, the feasibility of testing a newer application like PV was considered to be likely easier in children with DS and based on the findings the plan was to extend it to children with CVI.

Given the advantages of Peekaboo Vision application (PV app) we hypothesized that it would have good clinical utility for children with SEN. The main aim of this study was to determine the clinical utility of the PV in children with DS and to compare it with the commonly used Teller acuity cards-II

(TAC-II) (Teller et al., 2005 (revised)), which was noted to have comparable acuity measures as the Keeler acuity cards in typically developing children below 6 years of age (Neu & Sireteanu, 1997).

Methodology

Vision screening was conducted as part of the camp by a team of optometrists and ophthalmologists experienced in managing children with special needs. The study protocol was approved by the Institutional Review Board of L V Prasad Eye Institute and by City, University of London. The study followed the tenets of the Declaration of Helsinki. Informed written consent was obtained from parents before enrolling participants into the study.

Participants

In order to keep the testing uniform and taking into consideration that at least a few children were unfamiliar with optotypes, all participants were routinely measured with grating acuity. Chronologically similar aged controls with no obvious ocular conditions were also included. Control participants were recruited from a residential complex and Sunday school.

Clinical tools: A detailed description of TAC-II and PV app is already mentioned in section 2.2.1 and their thresholding paradigms are given in section 5.6.5.

Procedure

The presenting binocular visual acuity of children with DS and age-similar controls was measured by the examiner, as the purpose of the study was validating the tools. The sequence of tests were randomized prior to testing using a randomly generated table in Microsoft Excel. One examiner (PI) conducted both the tests but was masked to the stimuli. This examiner was helped by an observer who kept a record of the observations and the presented stimuli. The observer also helped in timing the test duration (using a stopwatch), handing over the charts/ replacing them and in noting down the child's responses as judged by the examiner. Retest was attempted on children with DS and on controls within an average duration of 2.5 months. Verbal feedback about the child's engagement with PV app was obtained from the parents.

Statistical analysis

Data was analyzed using IBM SPSS software (ver. 20, Chicago, USA). Paired tests were used, either parametric or non-parametric depending on the normality distribution of the outcome measure, i.e., visual acuity. $p<0.05$ was considered to be statistically significant. The 95% limits of agreement (LoA) between both tests were studied using Bland-Altman analysis.

Results

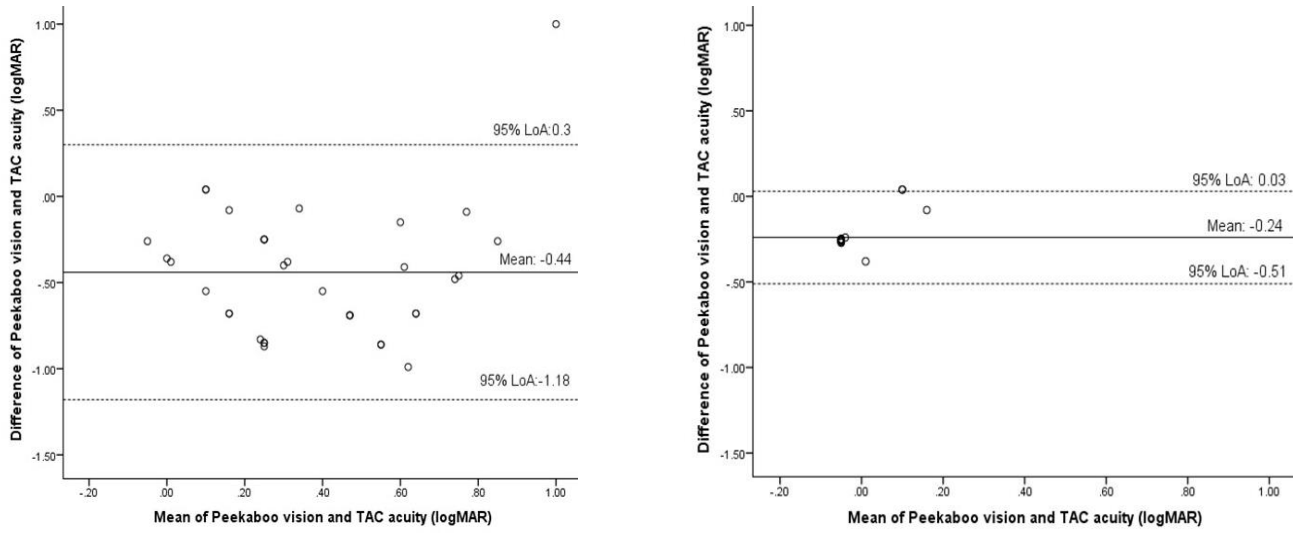
Thirty-seven children with DS and 19 chronologically age-matched controls were recruited in the study (table 4.3). Testability rates were similar for children using TAC-II and PV app (97%). The mean acuity with PV app and TAC-II were 0.16±0.34 and 0.63±0.34 logMAR respectively in the DS group. A significant difference was obtained between these two tests ($p<0.001$) (figure 4.2a). Retest was performed on 7 children with DS and on 4 controls. On retest, up to 3.5 lines [95% LoA (limits of agreement): -0.14 to 0.4 logMAR, CR: 0.35] variability was obtained with PV app and above 4 lines with TAC-II [95% LoA: -0.5 to 0.4 logMAR, CR:0.43] in children with DS.

In controls, testability rates were high for TAC-II and PV app (100%). the mean acuity with PV app and TAC-II were -0.15±0.09 and 0.08±0.00 logMAR respectively. A significant difference was obtained in controls between these two tests ($p<0.001$) (figure 4.2b). Retest in controls showed up to 3 lines variability with PV app [95% LoA: -0.37 to 0.33, CR: 0.33] and less than one line variability was noted with TAC-II [95% LoA: -0.1 to 0.1, CR: 0.08]. The time taken to complete PV app (mean=1.8±0.8 min) and TAC-II (mean=1.9±0.8 min) were comparable ($p=0.83$) in children with DS.

Demographic/Clinical parameter	**Children with Down syndrome (n=37)**	**Control group (n=28)**
Age (years) (Mean ± SD) Range	 8.1±4.2 1.3 to 17.0	 8.71±3.84 2.3-15.0
Gender (n, %) Males Females	 23 (62%) 14 (38%)	 15(54%) 13 (46%)
Testing duration (Mean ± SD) in minutes Peekaboo Vision app Teller acuity cards p-value	 1.8±0.8 1.9±0.8 0.83	 1.17±0.38 1.44±0.49 0.01

Table 4.3: Clinical and demographic characteristics of the participants

The interactive video feedback in the PV app was found to be a useful feature. All parents (100%) across both groups felt that the interactive feedback was helpful in maintaining their child's attention whilst carrying out the test.



(a) (b)

Figure 4.2: Bland-Altman plot representing 95% limits of agreement between acuity obtained using Peekaboo Vision app and Teller acuity cards-II in children with Down syndrome (n = 37) (4.2a) and in controls (n = 28) (4.2b)

(overlapping data points noted in 4.2b)

Discussion

Our findings suggest that there is potential to use PV app in measuring grating acuity in children with DS. We also noted that PV app over-estimated VA when compared to TAC-II in both groups of children. Mean logMAR acuities obtained with PV and TAC-II were found to be significantly different in children with DS (mean: –0.44 logMAR, 95% LoA: –1.18 to 0.3) and for controls (mean: –0.24 logMAR, 95% LoA: –0.51 to 0.03) ($p < 0.001$). The present study's control group acuity findings were comparable to the acuity differences obtained by Livingstone et al between PV app and Keeler acuity cards noted in the study (study 2: mean difference: 0.01 logMAR, 95% LoA: –0.413 to 0.437) that was carried out in typically developing children (Livingstone et al., 2019).

Some of the differences observed between the two tests may be related to their thresholding paradigms. The TAC-II uses the descending method of limits to present stimuli and responses obtained two out of three times were used to estimate grating acuity. The procedure is manual, and the step size (0.5 octave steps) may take longer before arriving at and refining the end point. Whereas, PV app uses an automated staircase paradigm which may be quicker and considerably more time efficient in arriving at the end point (Spielmann et al., 2013), this was evident in the control group in our study. A shorter testing time is desirable when assessing all children particularly non/preverbal and the younger age groups given their limited attention span. The difference could also be due to the larger jump in PV app acuity especially while thresholding at the finer grating acuity range (i.e., an incorrect response at –0.18 logMAR will have a 0.3 logMAR jump back to 0.12 logMAR) that accounts for an absolute difference of 0.3 logMAR. Another reason could be the uniform testing distance that was used for all age groups with TAC-II and PV app. According to the developer's guidelines, testing distance for TAC-II should be varied based on age (Teller et al., 2005 (revised)). However, to standardize the tests, a similar testing distance was used for TAC-II and PV app, for all participants. Hence the highest spatial frequency that could be recorded using TAC-II in the current study was 0.08 logMAR, which could have caused an artificial ceiling effect particularly for the control group. Children with DS are noted to have hypoaccommodation (Satgunam et al., 2019). The nature of the tests (print vs. digital) could have influenced the accommodation differently. However, the amplitude of accommodation was not investigated as part of this study due to its screening nature and the authors acknowledge this limitation.

Peekaboo Vision app has several advantages over paper-based traditional visual acuity tests which are worthwhile considering. It is easy to administer, is freely available and has high testability rates. Similar to TAC-II, 97% of children with DS and 100% of children in the control group were able to complete the test. It is also highly engaging, which would be particularly beneficial for children with special educational needs who tend to have a limited attention span. All parents of children who participated in the study gave positive feedback about the child's engagement with the app. The PV app can measure a range of acuities that would be particularly desirable on a population of children with special educational needs, who may present with a range of acuities. For example, at 50 cm, acuity measured ranges from –0.18 to 1.9 logMAR. By alternating the working distance, the range can be further expanded to –0.18 to 2.11 logMAR. In addition, as PV app application has an automated threshold, it is easier for even a novice examiner to carry out the test as in comparison to the experience that is often recommended to perform the test using conventional paper-based cards (Getz et al., 1996). However, this may be challenging if an inexperienced examiner has to judge responses based on the eye movements of the child and 'touch' the screen for the child. Good eye-hand coordination is needed to perform the test using the PV app. Children with special educational needs (e.g., with cerebral palsy) may have limited eye-hand coordination, which would make the task challenging. In such cases, the examiner should be able to judge the eye responses and touch the grating on behalf of the child.

Repeatability was noted to be within 1 octave (i.e., doubling/halving of the spatial frequency) using acuity card procedures in several studies in children with special educational needs (Mackie & McCulloch, 1995). A study by Livingstone et al (Livingstone et al., 2019) on typically developing children using PV app reported approximately three lines variability in both studies, i.e., in Malawi and the United Kingdom (study 1: 95% LoA: –0.283 to 0.198 logMAR, CR = 0.27; study 2: 95% LoA: –0.344 to 0.320 logMAR, CR = 0.32), which corresponds to less than 1 octave (i.e., 0.89 octave) and 1.06 octaves respectively. This was comparable to the present study in controls (1.09 octaves). Due to poor follow-up, only a small number of children with DS were recruited for a retest in this study which is a limitation.

The clinical testing time of the PV app was similar to that of TAC-II in children with DS. However, significant differences were found in controls. Testing times were significantly lower for controls

when they were tested with PV when compared to TAC-II. Possible reasons why the timings were similar for both tests in DS include the fact that because of eye-hand coordination problems some children with DS took much longer to touch the app and provide a correct response which delayed the test time. This was not a constraint for TAC-II as the examiner made the judgements, therefore even though TAC-II is constrained by the mechanical shifting of cards this may have offset the delayed judgement on the app giving similar testing times in DS. However, in controls where there are no motor constraints and judgments were made faster which could potentially result in shorter testing when compared to TAC-II, where the mechanical shifting of cards by the examiner and potentially a larger number of steps increased the time.

A larger sample size would be needed to determine the test-retest repeatability of PV app in children with DS and other disabilities. This would not only prove useful in the regular clinical testing of children with disabilities but also to quantify the true effect of any intervention using grating acuity.

Note: This paper has been published in the British and Irish Orthoptic Journal (Sumalini et al., 2022) (A3) and has been presented as a Scientific paper at the Vision 2022-the 13th International Conference on Low Vision Research and Rehabilitation

Key findings

- Peekaboo Vision app has the potential to be used in children with Down syndrome, particularly given its interesting feedback feature
- Peekaboo Vision app over-estimates acuity when compared to TAC-II in children with Down syndrome and age-similar controls
- The acuity estimates of Peekaboo Vision app and TAC-II are significantly different for children with Down syndrome and age-similar controls
- Potential reasons for differences in the acuity estimates are different thresholding paradigms and step sizes

4.4 Feasibility of using OKKO health app for measuring visual functions in young typically developing children

(Preliminary findings of OKKO health app is discussed below)

Introduction

In recent years, there has been a considerable increase in the use of mobile and tablet-based applications for visual function assessment (Satgunam et al., 2021). This has several advantages such as a viable option for patients to self-monitor their vision, portability and less maintenance when compared to card-based tests. Additionally, children are likely to show better interest in the app-based testing as they are gamified and therefore are likely to engage the child better when compared to a card-based test (Livingstone et al., 2019). One such application is the OKKO health app, developed by the OKKO health team, United Kingdom (Hardware-free games technology to accurately measure sight (OKKO health)). This app has undergone a few preliminary checks in children and adults by the developers *(unpublished results)*. However, it has not been tested for its feasibility in testing very young typically developing children. Through this study, we aimed to determine the feasibility of testing visual acuity (VA) and contrast sensitivity (CS) in children with CVI and in typically developing children using OKKO health. Suitable comparisons with other paediatric tests for VA using Teller acuity cards-II (TAC-II) and Peekaboo Vision app (PV app) and CS using Hiding Heidi cards (HH cards) and Ohio contrast cards (OCC) is also studied as part of this study.

Methods

A prospective cross-sectional study was carried out on children with CVI and on typically developing children in the age range of 6 months to 7 years recruited from pediatric neurology clinic of a tertiary children's clinic, and from residential complexes, Sunday school of a local church and a local children's home in Hyderabad, India. The presenting binocular VA were measured using OKKO-VA, TAC-II and PV app and CS using OKKO-CS, HH cards and OCC. Demographic data was also noted.

Instruments

OKKO health application –VA

The OKKO health software(Hardware-free games technology to accurately measure sight (OKKO health)) was used on the 11-inch iPad Pro with a screen resolution of 2388x1668, which included distance tracking using the TrueDepth camera. This screen size was chosen given the fact that this is the largest screen size on which the software is configured by the developers. The OKKO health includes two versions - a children and an adult version and configurations for specifically testing individuals with vision impairments. In this study, the children's version was used. There are tests for VA and CS using vanishing optotype principles that allow for a 'hidden object game' experience. All responses have audio and visual feedback upon touching the stimuli (circles for both VA and CS) (figure 4.3). The test could be paused at any time if needed during the entire duration of the test. Face identification was enabled in order to get cues about the testing distance throughout the duration of the test. The test is ideally recommended to be carried out at a testing distance of 30 cms. A green colour indication is displayed on the screen if the testing distance is appropriate (orange colour when the iPad is closer than the suggested distance and yellow colour if the iPad is placed further away than the testing distance). The examiner accordingly adjusted the testing distance based on this. The VA range that can be measured is: 1.04 to 0.04 logMAR.

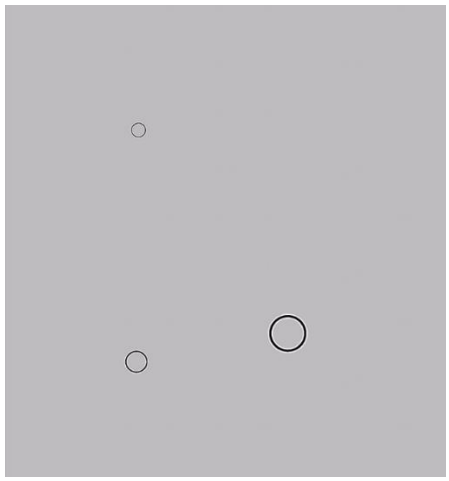


Figure 4.3: Visual acuity test using OKKO health application

OKKO health application-CS

The CS was tested by presenting eight levels of difficulty in two sets (set 1 = 1, 2, 3, 5, 7 and set 2 = 1, 2, 4, 6, 8), where 1 is the easiest (black) and 8 is the faintest). The RGB (Red Green Blue) values considered for stimuli were similar to the 8 values on the right-hand side of Pelli Robson chart, with the background remaining white all through (RGB value= 255). Five levels of contrast (either set 1 or set 2 first) appear simultaneously as bubbles or circles, and these bubbles float around the screen (figure 4.4) at 1cm/second. The task was to pop the bubbles. In cases where two overlapping bubbles were popped, the code considers the easier one as 'seen' and hence the more difficult one remains to stimulate a further reaction if visible. Each set appeared twice and the scoring system is such that RGB values seen were recorded and threshold was determined as the most difficult level which was seen twice. The total angle subtended by the contrast circle at 30 cms is 3.3 degrees, which was equivalent to 20/800 at that specific distance. The CS range that can be measured is: 0.00 to 2.25 logCS.

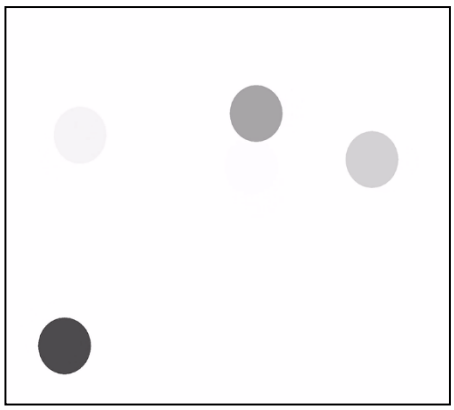


Figure 4.4: Contrast sensitivity test using OKKO health application

The description of other tests, TAC-II, PV app, HH cards and OCC is given in section 5.6.

Procedure

The examiner approached the parents/caregivers of the child and explained about the study using the participant information sheet. After checking their willingness to allow their child to participate in the study, the consent form was provided to the parents/caregivers to read through and consent as appropriate. In addition to English, the participant information sheet and the informed consent form

was also available in Hindi and Telugu, i.e., the two most commonly spoken regional languages in the city in which the study was conducted. In case of children who were recruited from the home for the homeless organization, the primary in-charge's consent was obtained. For all children verbal assent was also taken.

The VA and CS tests were randomized and no particular order of testing was followed. The testing times were noted for all the tests. In case of children who were unable to point out at the grating, based on their eye movements the examiner made the judgement of the location of the grating. However, this was not feasible while administering OKKO health app due to multiple stimuli presented at a time.

Results

OKKO health app was attempted in a total of 111 children with CVI (mean age: 3.00±1.85 years) and in 50 typically developing children. (mean age: 3.39±1.87 years; girls, n=21, 62%).

Children with CVI

OKKO health app had lower testability rate in children with CVI (15/111, 13.5%) when compared to controls. Further due to technical issues, the VA and CS recording was not available in 6 children. The mean VA for the remaining 9 children was 0.68±0.27 logMAR with a mean testing time of 1.37±0.39 minutes. The mean CS for these 9 children was 0.99±0.54 logCS with a mean testing time of 1.09±0.44 minutes. Due to the lower testability rate in children with CVI, further comparisons with TAC-II and PV app were not considered.

Typically developing children

Visual acuity testing

The testability rates, testing time using all the tests is summarized in table 4.4. Due to technical issues with OKKO Health app, the acuity and contrast scores of 9 children could not be recorded. The testing time was found to be significantly different across the three acuity tests (p-value: 0.03, Friedman test). On individual comparisons, OKKO Health-VA was found to take a significantly shorter time when compared to the PV app (p-value: 0.02) and TAC-II (p-value: 0.01). The youngest child who could participate in testing using OKKO health-VA and CS was 1.5 years old.

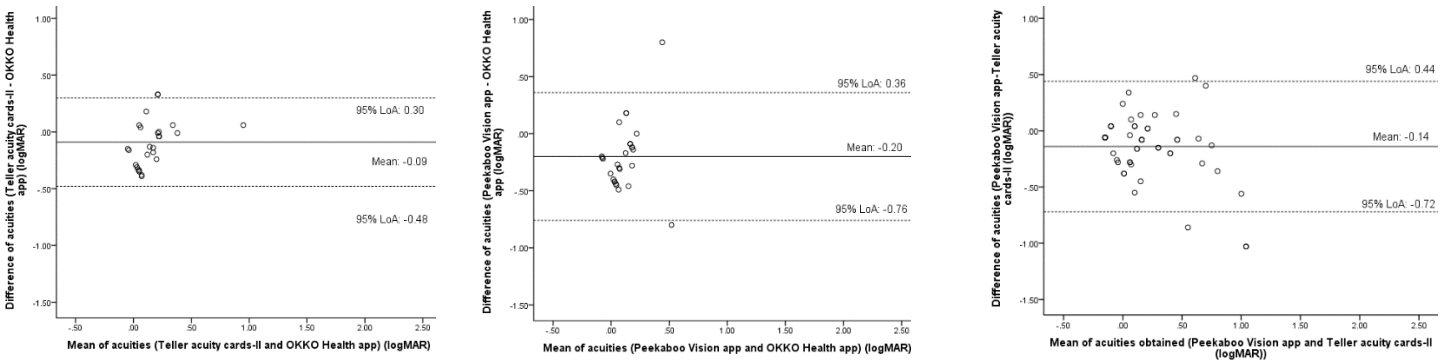
	Visual acuity (n=50)		Contrast sensitivity (n=50)		
Test	**Testability (%)**	**Testing time (mins)**	**Test**	**Testability (%)**	**Testing time (mins)**
OKKO Health-VA	36 (72%)	0.91±0.41	OKKO Health-CS	36 (72%)	0.78±0.38
Teller acuity cards-II	50 (100%)	1.44±0.64	Hiding Heidi cards	50 (100%)	0.53±0.38
Peekaboo Vision app	50 (100%)	1.23±0.51	Ohio contrast cards	50 (100%)	1.01±0.83

Table 4.4: Testability and testing times of tests of visual acuity and contrast sensitivity

The mean VA recorded using OKKO Health-VA was 0.21±0.17 logMAR (range: 0.02 to 0.92 logMAR) with TAC-II: 0.30±0.40 logMAR (range: -0.12 to 1.55 logMAR) and with PV app: 0.16±0.30 logMAR (range: -0.18 to 0.90 logMAR). The mean difference between the tests were noted to be: -0.09±0.2 logMAR between OKKO Health-VA and TAC-II (95% LoA: -0.48 to 0.30 logMAR, p=0.02); -0.20±0.29 logMAR between PV app and OKKO Health-VA (95% LoA: -0.76 to 0.36 logMAR, p=0.01). -0.14±0.30 logMAR between PV app and TAC-II (95% LoA: -0.72 to 0.44 logMAR, p<0.001). (figure 4.5) The mean acuities with the tests and their ranges have been summarized in table 4.5.

Test	Mean±SD (logMAR)	Range (logMAR)
OKKO Health (n=27)	0.21±0.17	0.02 to 0.92
TAC-II (n=50)	0.30±0.40	-0.12 to 1.55
Peekaboo Vision app (n=50)	0.16±0.30	-0.18 to 0.90

Table 4.5: Mean and range of acuities obtained using tests of visual acuity



(a) (b) (c)

Figure 4.5: Bland-Altman plots of agreement between OKKO health-VA and TAC-II (a) (n=27), OKKO health-VA and Peekaboo Vision app (b) (n=27) and TAC-II and Peekaboo Vision (c) (n=50)

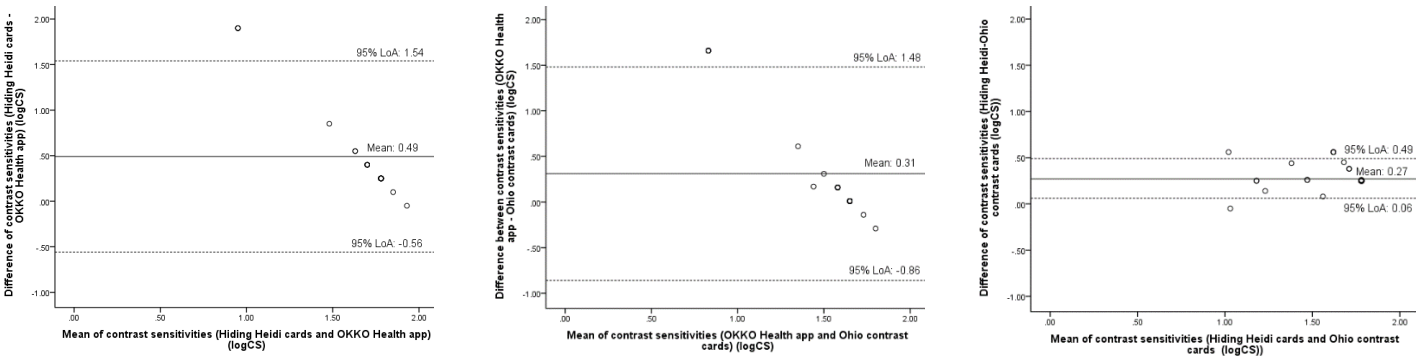
Contrast sensitivity testing

The testing time was found to be significantly different across the three CS tests ($p<0.01$, Friedman test). On individual comparisons, HH cards were found to take a significantly shorter time when compared to OCC ($p<0.01$) and OKKO Health ($p<0.01$). OKKO Health was found to take a significantly shorter duration when compared to OCC ($p= 0.01$) (table 4.4).

The mean CS recorded using OKKO Health-CS was 1.58±0.17 logCS (range: 1.05 to 1.95 logCS), with HH cards was 1.81±0.21logCS (range: 1.00 to 1.90 logCS) and with OCC was 1.54±0.21 logCS (range: -0.74 to 1.66 logCS). The mean difference between the tests were noted to be: 0.49±0.54 logCS between OKKO Health-CS and HH cards (95% LoA: -0.56 to 1.54 logCS, $p<0.001$); 0.31±0.6 logCS between OKKO Health-CS and OCC (95% LoA: -0.86 to 1.48 logCS, $p=0.002$) and 0.27±0.1 logCS between HH cards and OCC (95% LoA: 0.06 to 0.49, $p<0.001$); (figure 4.6). The mean CS obtained and their ranges have been summarized in table 4.6.

Test	Mean±SD (logCS)	Range (logCS)
OKKO Health (n=27)	1.58±0.17	1.05 to 1.95
Hiding Heidi cards (n=50)	1.81±0.21	1.00 to 1.9
Ohio contrast cards (n=50)	1.54±0.21	0.74 to 1.66

Table 4.6: Mean and range of contrast sensitivities obtained using tests of contrast sensitivity



(a) (b) (c)

Figure 4.6: Bland-Altman plots of agreement between OKKO health-CS and Hiding Heidi cards (a) (n=27), OKKO health-CS and Ohio contrast cards (b) (n=27) and Hiding Heidi cards and Ohio contrast cards (c) (n=50)

Discussion

These preliminary results demonstrate the feasibility of using OKKO health app in young typically developing children to assess VA and CS and also the challenges involved in assessing children with CVI. The testability rates of OKKO health-VA and CS was 72% which was lower than standardized charts such as TAC-II (94%) (Leone et al., 2014) and Keeler acuity cards (98.9%) (Neu & Sireteanu, 1997) in almost similar aged typically developing children. Similarly the testability for OKKO health CS (72%) was found to be lower than picture-based HH cards (100%) (Leat & Wegmann, 2004). This could be primarily attributed to the different nature of the tasks. Other than OKKO health-VA and CS, all the other tests of VA and CS use preferential looking technique, either grating or picture-based. In infants and very young children (6 months to 1.5 years), who were unable to point out at the grating or the picture, based on their eye movements the examiner made the judgement of the location of the gratings/picture. However, this was not feasible in case of OKKO health app due to multiple stimuli being presented at a given time.

The testing times were noted to be shorter using OKKO health-VA when compared to TAC-II and PV app which is very desirable while testing very young children (Sumalini et al., 2022). Acuity estimates using OKKO health-VA was noted to be closer to TAC-II findings when compared to PV

app. However, in case of CS the difference was noted to be smaller between HH cards and OCC when compared to OKKO health-CS app. This could be attributed to the different step sizes that the tests measure and the different nature of the tasks.

Responding by clicking on the screen needs good eye-hand coordination, which is likely to be challenging in in very young infants, but at the same time was observed to be very engaging for the older children. In addition to the gamified method of testing used in OKKO health app, the audio feedback feature during the assessment with the app, was also observed to help the children to be attentive to the task.

Considerations for children with special educational needs

The testability rate of OKKO health app among children with CVI was very poor in the current study (13.5%). This can be largely attributed to the task requiring good eye-hand coordination to pop the balls, which is likely to be affected in children with CVI. Multiple stimuli being presented at once makes the judgement difficult for the examiner in case the child is unable to perform. This is very similar to what was observed in very young children (i.e., <1.5 year-olds) in the typically developing children as well. Given the interesting features of this app, it can be further explored in children with special educational needs above 1.5 years old (such as in Down syndrome and autism spectrum disorder). It may be challenging for children with motor restrictions, such as cerebral palsy and cerebral visual impairment to perform the task (Chokron & Dutton, 2016). The recommended testing distance is at 30 cms and therefore it was easier for young children to touch the screen by themselves. However, this close testing distance stimulates accommodation and children with certain causes of special educational needs such as CVI (Pehere et al., 2019) and Down syndrome (Satgunam et al., 2019) could have hypoaccommodation, which should be considered while interpreting the findings.

Through this preliminary work, we could demonstrate the feasibility of using OKKO health app in young typically developing children (≥1.5-year-old) to assess VA and CS. In few children the scores could not be recorded, due to technical issues as the app is still in its development phase. The OKKO health app offers interesting features to assess VA and CS in a gamified testing method, thereby making the assessment process less challenging and less demanding to have a trained examiner.

However, a couple of recommendations that could be considered for assessing children with special educational needs include restricting the number of stimuli displayed at a given time and an option to adjust the movement of the stimuli can be provided to the examiner. Further research is warranted to understand the clinical utility of OKKO health app and by comparing the findings with standardized charts in a larger sample of typically developing children to establish normative data.

Key findings

- OKKO health app was testable in typically developing children ≥1.5-year-old (72%)
- However, OKKO health app was noted to have lower testability in children with CVI (13.5%)
- Lesser number of stimuli displayed and option to adjust movement of the stimuli can be useful to help test children with special educational needs

4.5 Selecting tests to validate in children with cerebral visual impairment in the current study

The findings of preliminary study 1 reveal that VA, CS and peripheral visual fields are the most affected in children with SEN. However, the availability of clinical tools for testing the paediatric group with SEN is limited to tests of VA and CS. Therefore, these two visual functions were selected to be tested in this study. The preferential looking technique has proven to be a useful and a well-established method of eliciting responses for VA testing in children with special needs (Mackie & McCulloch, 1995). The success rates for testability using preferential looking technique has varied between 57.5% (Chandna et al., 1989) and 100% (Adams & Courage, 1990) in previous studies. This wide range of success rates is likely due to the diverse cohort of special educational needs included in the study population (e.g., adult group with varying degree of impairment, however, causes were not specified) (Chandna et al., 1989). A majority of these studies have reported a testability rate of over 70% (Mackie & McCulloch, 1995).

Resolution tasks using gratings are particularly useful in measuring visual functions in pre-verbal/non-verbal children (LEA (Grating acuity tests), edited in 2009). However, these tests were noted to over-estimate acuities when compared to using letter optotypes in children aged 8 years and below with non-strabismic anisometropic amblyopia. Worsening of grating acuity was not noted with proportionate worsening of letter acuity (Friendly et al., 1990). Larger discrepancies in acuities between the tests were found in children with dense amblyopia and foveal disorders. Possible reasons include differences in ocular pathologies, single vs. line acuity, size of the stimulus and the relative complexity of the stimulus (Mayer et al., 1984). Intra-examiner repeatability was found to be better with a letter chart ($r=0.95$, Pearson product moment correlation) when compared with Teller acuity cards ($r=0.68$, Pearson; $r=0.80$, Spearman rank) (Friendly et al., 1990).

However, given the nature of the population to be tested in the current study and their age ranges (6 months to 7 years), a letter-based measurement of visual function would not be appropriate, i.e., although more repeatable, but may not be feasible in the current study cohort. From the literature review it is clear that the preferential looking technique provides a valid alternate measurement to consider in these children based on limitations imposed by their age and condition. Traditionally most preferential looking techniques have been paper-based but recent advances mean that these are now available on a variety of devices such as computers (e.g., Automated visual acuity test) (Vrabic et al., 2021) and tablets (e.g., Peekaboo Vision app) (Livingstone et al., 2019). Computer-generated charts were found to be comparable in terms of repeatability, testing time and accuracy when compared to traditional paper-based charts for both high and low contrast charts. The added advantages of manipulating the contrast, changing the letters, adjusting other testing options are all in the favour of

computer-generated charts (Ehrmann et al., 2009). Additionally, the current generation of children are well adapted to technology and given some of the advantages of tech-based tests, one of the most important being the gradual move towards the home-monitoring of the visual functions, we felt it was important to identify two tests for each visual function, one that was paper-based and one that was deliverable on a tablet. In the current study, we will be validating the well-established TAC-II (Mash & Dobson, 1998) and comparing it to the PV app. The clinical utility of this app has been tested in typically developing children and in those with vision impairment (Livingstone et al., 2019).

The choice of test proved reasonably easy for VA, however, we encountered some difficulties with CS, primarily due to limited availability of CS tools for paediatric cohort. The OCC that use grating stimuli had been clinically tested in children with vision impairment (Hopkins et al., 2017). Therefore, OCC was chosen to be compared against the most commonly used clinical test in the paediatric group, the HH cards.

We also tested the feasibility of the newly developed OKKO health app (for both VA and CS) in children with CVI and age-similar typically developing children. Preliminary testing revealed that children with CVI had poor testability rate, however, it was feasible to test ≥1.5 year old typically developing children. Considering these findings, we did not include the OKKO health app as a part of the main study.

Chapter 5 : Methodology

5.1 Chapter overview

The previous chapters, specifically chapters 1 and 2 covered what is already known in the field of special educational needs, particularly in children with CVI. It is important to note that SEN is a diverse group, including CVI which in itself can present in varying degrees of severity. Therefore, in order to understand the basic visual functions (such as VA and CS) appropriately, it is important to understand that these functions can be influenced by factors beyond chronological age and refractive errors as seen in typically developing children. While VA and CS have been used as outcome measures in a small minority of studies discussing intervention measures in children with CVI (Delay et al., 2023), the correct interpretation of these results are crucial for clinicians, rehabilitation therapists, neurologists and ultimately to the family members for prioritizing and better planning. With this understanding, we will revisit the primary aim of the current study, i.e., validation of clinical tools of visual functions in children with CVI. In order to interpret this appropriately, we have established the following five study objectives (also mentioned in section 3.3):

Study objectives:

1. *To describe the demographic and clinical characteristics of children with CVI and age-similar typically developing children.*

2. *To determine the limits of agreement between two tests of grating VA, i.e., Teller acuity cards -II (TAC-II) and Peekaboo Vision application (PV app) in children with CVI and compare with age-similar typically developing children.*

3. *To determine the limits of agreement between two tests of CS, i.e., Ohio contrast cards (OCC) and Hiding Heidi cards (HH cards) in children with CVI and compare with age-similar typically developing children.*

4. *To determine the intra-observer repeatability of two different VA (TAC-II and PV app) and CS (OCC and HH cards) tests in children with CVI and in age-similar typically developing children*

5. *To determine the association of the visual functions with developmental quotient, seizure history and activity, brain imaging findings and functional vision measure in children with CVI.*

This chapter describes the methodology that is employed for the current study for the above-mentioned study objectives.

5.2 Study design

A prospective, case-control study was carried out in the neurology clinic at Rainbow Children's Hospitals (a tertiary multispecialty hospital), Hyderabad, India and L V Prasad Eye Institute, Hyderabad, India. This study design was chosen in order to take all possible confounding factors into consideration such as seizures and related medication, developmental quotient, MRI findings while measuring outcome factors, i.e., VA and CS and functional vision score.

5.3 Ethics approval

Ethics approval was obtained from the Institutional Review Board at LVPEI, Hyderabad, India; the Optometry Proportionate Review committee at City, University of London, UK and the Institutional Review Board at Rainbow Children's Hospitals, Hyderabad, India to conduct this study. The study adhered to the tenets of the Declaration of Helsinki. The participant information sheet was read by the parents/caregivers or read out by the PI for those parents/caregivers who were unable to read *(the PI was familiar with all the 3 languages)*. This was followed by obtaining written informed consent from the parents/caregivers if they were willing for their child to participate in the study in the language that they understood, i.e., for a majority in the regional language Telugu (n=77, 69.3%), for some in Hindi (n=31, 27.9%) and for a small number of parents in English (n=3, 2.7%). Verbal assent was obtained from the child wherever possible For controls, either parents (n=31,62%) signed the informed consent or the person in-charge for children in the local children's home (n=19, 38%), after explaining the study purpose in the language that they understood, Telugu (n=31, 62%) and English (n=19, 38%). Verbal assent was obtained from the child wherever possible.

5.4 Participants

Children aged 6 months to 7 years with a confirmed diagnosis of CVI due to common aetiologies such as hypoxic ischemic encephalopathy (HIE), neonatal hypoglycaemic brain injury (NHBI), periventricular leucomalacia (PVL) and genetic causes (such as (KCNQ2 encephalopathy (Milh et al., 2013), B3GALNT2 mutation (Maroofian et al., 2017) (Philip & Dutton, 2014) were recruited in the study. It is recommended that the diagnosis of CVI only be made after the child is at least 6 months of chronological age (How Doctors Diagnose CVI? (PCVIS)). Until then the child is

provisionally diagnosed to have delayed visual maturation with other developmental delays. Considering the critical period of the visual cortex development is upto ~6-8 years of age for acquired amblyopia (Gunton, 2013), the upper age limit of 7 years was chosen.

The control group included chronologically age-matched children with no obvious vision impairment (either ocular or cerebral) and those having chronologically age-appropriate developmental milestones as mentioned by parents/primary caregiver and through PI's observation.

5.5 Sample size

The formula for sample size for agreement studies (McAlinden et al., 2011) was used to calculate the sample size in the current study.

$$1.96\ \sqrt{(3s^2)}/(n) = \text{Desired confidence interval of limits of agreement}$$

The standard deviation of the differences between measurements by the 2 methods[9] was taken as 0.37 logMAR and the desired confidence interval of limits of agreement (LoA) was considered as 0.3 logMAR. These estimations were based on the pilot study carried out on a cohort of children with SEN (see section 4.3). The required sample size was estimated to be 50 children each in three main aetiologies of CVI, i.e., HIE (Pehere et al., 2018), NHBI (Paudel et al., 2017; Tam et al., 2008) and PVL (Jasper & Philip, 2018) and also 50 age-similar typically developing normally sighted children as controls.

5.6 Instruments

5.6.1 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is the diagnostic test of choice for children with CVI and can detect lesions caused by HIE and PVL, that may go undetected on ultrasound scans (Triulzi et al., 2005). The findings from neuroimaging have been used in the current study for grading the severity of brain damage based on the location and extent. The grading used by Cioni et al in 1996 is given in table 5.1 (Cioni et al., 1996). This grading scale was found to have a strong correlation with MRI findings and the extent of the vision impairment in children with neonatal encephalopathy (Cioni et al., 1996). However, this scale does not grade the location (unilateral or bilateral) and extent (such as small, large; segmental or diffuse) of the injury in detail. Further revisions to this grading were

[9] *2 methods include acuity measurements with Teller acuity cards-II and Peekaboo Vision app*

carried by Cioni et al in 2000 by including several other parameters (table 5.2) (Cioni et al., 2000). This revised criteria along with few changes as deemed appropriate by an experienced neurologist (LL) and neuro-radiologist (NR)) are being used in the current study and graded by an experienced neuro-radiologist with 5+ years' experience of using this grading. The cumulative score of the parameters is then used to categorize the child into mild (1 to 9), moderate (10-18) or severe (19 to 27) based on the MRI findings of the brain.

Optic radiations classification		
Grading	**Interpretation**	**Description**
I	No impairment	Optic radiations observed on the axial and coronal areas
II	Moderate impairment	When areas of abnormal signals, hiding the optic radiations, were found near the ventricular walls
III	Severe impairment	When areas of abnormal signals also involved the surrounding white matter
Visual cortex (involving striate, parastriate and peristriate areas) classification		
Grading	**Interpretation**	
I	Normal	
II	Impaired	

Table 5.1: MRI classification based on the findings noted in the coronal and axial planes
(Source: Cioni G et al, 1996) (Cioni et al., 1996)

Abnormality	**Grading**	**Description**	**Scoring**
Size of lateral ventricles	Grade 1	Normal	0
	Grade 2	Mild Unilateral or Bilateral	1
	Grade 3	Moderate to severe	2
WM signal	Grade 1	Normal	1
	Grade 2	Focal-PV-WM	2
	Grade 3	Bilateral	3
WM reduction	Grade 1	Not reduced	1
	Grade 2	PV-WM/unilateral deep WM	2
	Grade 3	Bilateral deep WM	3
Cysts	Grade 1	No cysts	1
	Grade 2	Unilateral	2

Abnormality	Grading	Description	Scoring
	Grade 3	Bilateral	3
Corpus callosum	Grade 1	Normal	1
	Grade 2	Segmental thinning	2
	Grade 3	Diffuse thinning (>3 segments)	3
Cortical matter (other than visual cortex)	Grade 1	No	1
	Grade 2	Unilateral	2
	Grade 3	Bilateral	3
Thalamus	Grade 1	Normal	1
	Grade 2	Unilateral	2
	Grade 3	Bilateral	3
Optic radiations	Grade 1	Normal	1
	Grade 2	Unilateral	2
	Grade 3	Bilateral	3
Occipital lobe/visual cortex	Grade 1	Normal	1
	Grade 2	Unilateral	2
	Grade 3	Bilateral	3

Table 5.2: Revised MRI grading scale used in this study
(WM=White Matter, PV=Periventricular)

5.6.2 Denver Developmental Screening Test 2nd edition (DDST - II)

This tool has been used in the current study to formally assess developmental skills in children with CVI, as the developmental milestones are likely to be delayed in this cohort (Pehere et al., 2018). The test is recommended to be administered to children upto 6 years of age (Frankenburg et al., 1992a), however a couple of studies have used the instrument in children aged 6-7 years as well (Frankenburg et al., 1992b; Wijedasa, 2012). In the current study, the instrument was used in children upto 7 years of age, after seeking advice from an experienced clinical psychologist performing developmental quotient assessments with over 20+ years of experience. This test takes approximately 20-30 minutes to administer and interpret the results. The four domains that are assessed in the test include fine motor-adaptive, gross motor, personal-social and language skills. The fine motor-adaptive skills include tasks involved with eye-hand coordination, such as manipulation of small objects. Examples of gross motor tasks include sitting, walking, jumping and other muscle coordination tasks. The personal-social tasks include interacting with people and also caring for personal needs in older children and in case of infants they were scored based on

responsive smiling, regarding his/her own hand. The language skills comprise of hearing, comprehending and using language for communication purposes (Frankenburg et al., 1992a). The DDST-II was found to have good predictive accuracy on children as young as 6 months (sensitivity=100% and specificity=95%) and was therefore chosen as an appropriate test for the current study (Hallioglu et al., 2001).

The DDST-II includes 125 items that are based on the child's performance and parental report (see appendix (A13)). Scoring is carried out on a 4-point rating scale that includes pass, fail, no opportunity to do the task and refusal to perform the task. The score is generated relative to normative data for that particular age placing each child in a percentile rank. The normative data for this test was generated from 2096 typically developing children from Denver, USA. Although the validation of this tool had been undertaken in a cohort of children from the USA, the tool has been used in several other groups of children belonging to various other geographical locations as well (Nair et al., 2009; Shahshahani et al., 2011; Sudry et al., 2022). Differences due to milestone evaluation methods and the cultural discrepancies can play a role in establishing the normative data across different ethnicities (Wijedasa, 2012). However, this scale was chosen as it is widely used by healthcare practitioners globally including India (Wijedasa, 2012). The percentile ranks for this test includes 25^{th}, 50^{th}, 75^{th} and 90^{th}. The chronological ages of the children are adjusted for prematurity accordingly. The individual items can be interpreted as advanced, normal, caution, delayed or no opportunity. The test results as a whole yield a normal, suspect or untestable outcome. In regular clinical practice, it is advisable to retest the child again after 1-2 weeks in case the result is 'suspect' or 'untestable'. In situations where the child is classified as suspect or untestable, they are referred for early intervention services (Frankenburg et al., 1992a). Early intervention services consists of therapies including physiotherapy, speech and hearing therapy, special education, occupational therapy and vision therapy. It also includes parental counselling, training and support groups. The developmental quotient/age assessment will be carried out only once on the child in the first visit and no retest will be performed given the financial and logistical constraints (as each session will take around 1.5 hours to complete). As DDST-II only has normative data up to 6 years of chronological age, the developmental psychologist used normative guidelines form the Developmental Screening Test (Bharatraj, 1983) for those children who were >6-7 years, which was relatively a small proportion (n=8, 14%). As both tests are fairly similar it was agreed by consensus of the research team and the developmental psychologist that this was an appropriate approach to follow.

5.6.3 CVI range instrument

The CVI range instrument (see appendix (A14)) has been used in the current study to measure the functional vision of children with CVI. This includes aspects of functional vision that help clinicians and rehabilitation professionals understand the severity of CVI on day-to-day visual functioning. This tool was developed by Roman-Lantzy in 2007 and includes characteristics that are unique to children with CVI (mentioned in section 1.5.8) (Newcomb, 2010). These characteristics are assessed through direct assessment (figure 5.1), observation or by interviewing the parent/caregivers. Two rating scales (for the same characteristics) are used as part of the CVI range: (i) across-the- characteristics scale (i.e., an overall understanding of the child's visual abilities) and (ii) within-the-characteristics scale (i.e., rating of each characteristic to understand the extent of the individual contribution of each characteristic to the overall visual functioning of the child). It is suggested to use both rating scales to draw the final score. However, scores from both rating scales may not be identical but are usually similar (Roman-Lantzy, 2018). In a separate study carried out by rehabilitation professionals from LVPEI, administering across-the-characteristics scale was noted to be time taking (approximate range: 40 minutes to 1 hour) (unpublished results). Therefore, for the purposes of this study, only within-the-characteristics rating has been carried out and used as surrogate measure, primarily due to time constraints. In within-the-characteristic rating scale, each characteristic is scored on a 0.25 interval ranging from 0 to 1.0. The cumulative score is in the range of 0 to 10.0. With 0 indicating 'no visual responses' and 10.0 indicating 'near normal or normal visual responses.' Based on the final score the child is categorised into any of the 3 phases: (i) building visual behaviour (score range: 0 to 3.0), (ii) integrating vision with function (3.25 to 7.0) (iii) resolution of CVI characteristics (7.25 to 10.0) (Newcomb, 2010).

Figure 5.1: Visually guided reach characteristic testing as part of functional vision assessment using CVI range instrument

(Note: Photo consent obtained from the parent)

5.6.4 General COVID-19 related precautions that were followed in this study

The data collection for the study commenced from October 2020 to October 2022. All precautionary measures were taken throughout the entire study period. Data collection of children with CVI and control group was carried out using COVID-related clinical protocols. The PI and the other observer used personal protective equipment such as a face mask, protective apron and hand gloves. Frequent sterilization of the hands using an alcohol-based hand disinfectant - Sterillium® (having a total alcohol concentration of 75%) (Sterillium: Frequently asked questions (Surgikleen)) was performed after every participant and in between the tests as well. The importance of wearing a face mask was emphasized to parents/caregivers and children. The usage of personal protective equipment was very important as the visual function tests were carried out at a close working distance (ranging from 25 to 84 cms). Children's hands were sanitised using an alcohol-based disinfectant Sterillium® before and after testing when electronic tests were used, as they would touch the screens. Physical distancing norms were strictly followed while explaining about the study protocol and while obtaining informed consent. The pen, tabletop and door handle were sterilized after every patient using Sterillium®. The completed consent forms and data sheets were placed separately in a folder and handled after a minimum duration of 72 hours, in order to reduce the exposure to the virus that can remain in an active state on the surface for a period of 72 hours.(Study suggests new coronavirus may remain on surfaces for days (NIH Research Matters),

2020) Minimal equipment was placed in the examination room to minimize sterilization time after every participant.

5.6.5 Visual acuity and contrast sensitivity tests

Visual acuity was tested using TAC-II and PV app. Contrast sensitivity was determined using OCC and HH cards. The reasons for selecting these tests had been discussed in section 4.5. These tests were used in a randomized order and the sequence of the tests was noted. In case of children crying or not cooperative at the start of the testing, the electronic test (in the current study, PV app) was first shown to pacify them and grab their attention (n=10). The testing of the visual functions was done binocularly and with habitual correction, if any. The binocular presenting VA and CS was preferred in the current study in order to avoid longer chair time for the children and given that the research question was primarily about the validation of the clinical tools. The description of these tests had already been mentioned in section 2.2.1 and the methods followed in the current study have been described here. This section gives an understanding of the testing protocol used in the current study.

Testing protocol for the visual functions

Both the acuity and contrast tests have been carried out binocularly and with the child's habitual correction, if any. The acuity and contrast testing was also randomized in addition to randomizing the order of testing of the 2 acuity and the 2 contrast tests. Children were encouraged to touch the screen or point to the target based on the nature of the test. In case the required response was not achieved in terms of touch/pointing out, the PI relied on the child's eye movements to finalize the response for any particular stimulus shown.

Visual acuity tests

Teller acuity cards (TAC-II)

In the current study, the TAC-II was used without the testing stage. The main purpose of the stage is to cut down the visual clutter in the background and keep a uniform grey background similar to the cards. However, the use of the stage in this study was deferred as it was difficult to comfortably position children with CVI in front of the stage due to their varied severity of developmental delays (especially motor delays). Testing without the stage could have caused some amount of distraction to the child, which was taken care of by having visual clutter free testing space, as far as possible practically. Very young children, i.e., 3 years and below were seated on the parent/caregiver's lap.

Children above 3 years who were willing to sit on the chair by themselves, were encouraged to do so (figure 5.2). However, as children with CVI have motor delays, it was not always possible to determine their seating preference based on the chronological age and therefore flexibility was used in our approach.

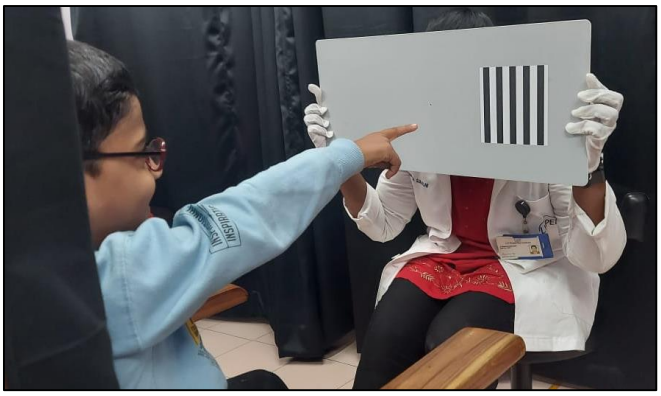


Figure 5.2: Visual acuity testing using Teller acuity cards-II

(Note: Photo consent obtained from the parent)

Visual acuity values obtained both with and without the testing stage were found to be within the age-appropriate norms in typically developing children at 3 different age groups of 3.5, 11 and 30 months (Clifford-Donaldson et al., 2006). A minimum of 10 cd/m^2 (candela per square metre) is suggested for acuity assessment using TAC-II with overhead diffuse fluorescent lighting in the room (Teller et al., 2005 (revised)). In the current study, the mean chart luminance was 72±9 cd/m^2. As recommended in the TAC-II manual, the testing distance was varied based on the chronological age of the child, in order to compare the acuity values with similar chronologically aged typically developing children. The three testing distances that were used were 38 cms, 55 cms and 84 cms (table 5.3) (Teller et al., 2005 (revised)). The PI presented the cards in descending order starting from 0.23 cycles per centimetres (CPCM) to 26.0 CPCM and another observer documented the child's responses as interpreted by the PI. Initially a test distance of 55 cms was chosen for presentation, then based on the response it was either decreased (38 cms) or increased (84 cms). If the child gave the correct response to the presented grating, (i.e., by PI verifying the response whether it was correct or incorrect by looking at the card after documenting the child's response of right or left) the PI then proceeded towards the immediate next card (i.e., towards higher spatial frequency). If the child gave a different response to the actual orientation of the grating, then that card was shuffled and presented 1 more time and the response that was obtained 2 out of 3 times

was considered. If the child was not/incorrectly responding to a particular card 2 out of 3 times, then the card that was shown earlier was presented again for confirming and the response was noted. This was considered as the end point of the test (figure 5.3).

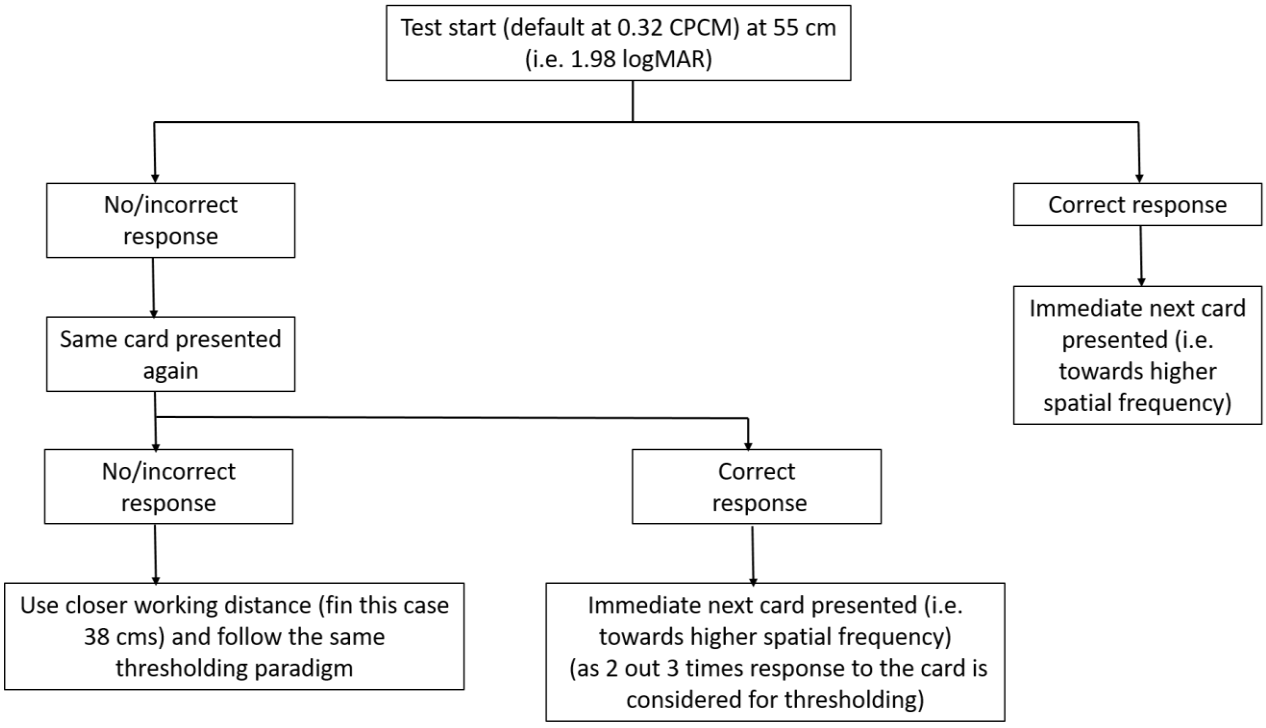


Figure 5.3: Flow chart explaining the thresholding paradigm followed for Teller acuity cards-II

Peekaboo Vision application

In the current study, PV app (version 1.5) was used on a 12.9 inches (2nd generation) iPad Pro with a screen resolution of 2732x2048. The larger screen size was chosen as participants were likely to have reduced VA given their diagnosis and this combination of screen size and resolution allows for greater size and testing combinations. During the development process of the tests, the mean screen luminance of 108.7 cd/m^2 (SD 8.9) at 50% brightness to 298.7 cd/m^2 (SD 25.1) at 100% range was found to be suitable for clinical testing, hence PV automatically defaults to 75% brightness, and impedes screen brightness below 50% (User manual (version 1.5); Peekaboo Vision: High Frequency Grating Infant Acuity, 2016). In the current study, the mean luminance was measured to be 153±8 cd/m^2. The iPad was switched on atleast 15 minutes prior to the testing in order for the screen luminance to completely stabilize. The distance between the child's eyes and the tablet was set for a range of 25 to 50 cms. As part of testing using the PV, it was preferable for the child to touch the screen to indicate the response (figure 5.4). However, in instances where the child's arm

length was shorter than 50 cms, the examiner moved the screen closer and the acuity score was automatically varied (auto correct for distance) on the main menu screen based on the test distance. The testing distance used was maintained by using manually placed markings indicating the distance. The iPad was held by the PI at the eye-level of the child and the distance between the iPad screen (anterior most) to the child's eyes was measured, documented and accordingly set on the iPad. In case the child was unable to touch the screen for reasons such as limitations in upper limbs (in children with CVI) or unwillingness to touch (such as in controls), the child's response based on his/her eye movements to the presented grating was observed by the PI and the PI touched the screen in order to progress the test. This was documented by the PI. The two-forced choice preferential looking paradigm was used for all children as judging the eye movements was very difficult when more than two choices are presented to children with CVI, especially as sometimes the judgement had to be made by the PI based on the child's eye movements. This choice was appropriate as TAC-II also is a 2-AFC test and comparisons will be easier.

Figure 5.4: Visual acuity testing using Peekaboo Vision application

(Note: Photo consent obtained from the parent)

The spatial frequency ranged between -0.18 logMAR to 2.11 logMAR (table 5.3). By default, the testing starts from 1.3 logMAR unless selected otherwise. As described earlier (see section 2.4), PV follows the staircase method of presenting the gratings with a three-line logMAR jump (or 1 octave-jump). However, for each incorrect response the same grating was presented 2 times more and the response that was obtained 2 out of 3 times for that particular grating was taken. Following this one logMAR progression, the immediate next lower spatial frequency was displayed and was followed from thereon in one logMAR step (figure 5.5) (User manual (version 1.5); Peekaboo Vision: High

Frequency Grating Infant Acuity, 2016). For example: If the child had correctly responded to the 1.00 logMAR grating that had been presented, the next grating was displayed (i.e. 0.72 logMAR) and the responses obtained 2 out of 3 presentations was considered. If the response is incorrect 2 out of 3 times for 0.62 logMAR, the immediate next lower spatial frequency grating of 0.72 logMAR was presented.

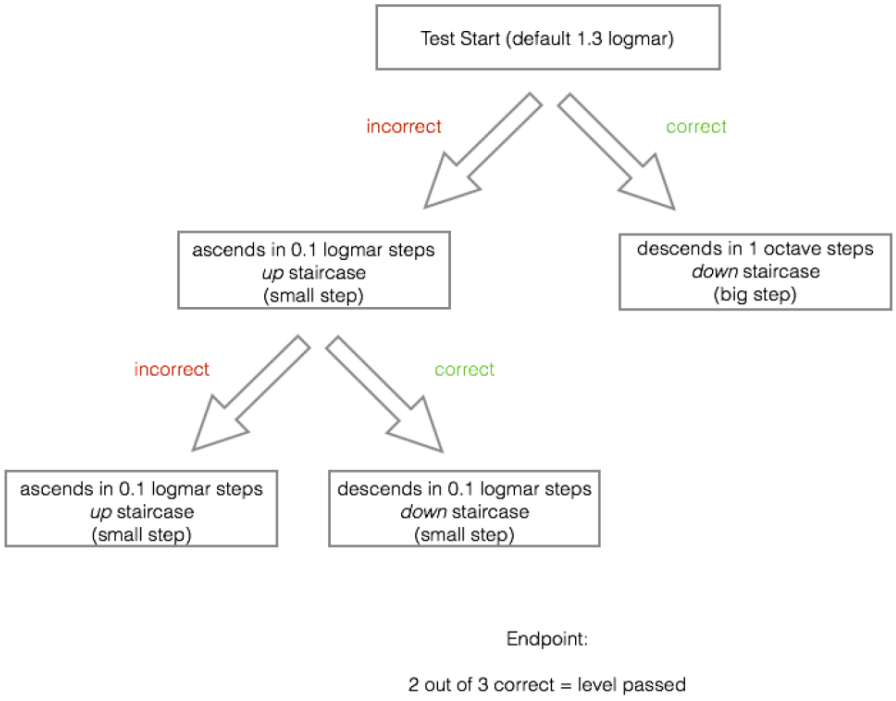


Figure 5.5: Flow chart explaining the staircase method followed in Peekaboo vision application *(Source: User manual: Peekaboo vision)*

Visual acuity test	**Test distances (cms)**	**Range of testable visual acuities (logMAR)**
Teller acuity cards-II	38, 55 and 84	2.30 to -0.12
Peekaboo Vision app	25 to 50	2.2 to -0.18

Table 5.3: Visual acuity tests with their test distances and range of testable visual acuities

Contrast sensitivity tests

Hiding Heidi low contrast face test

Hiding Heidi low contrast face test *(referred here as Hiding Heidi cards-HH cards)* have been used in descending order in this study. The test follows the 2-alternate forced choice preferential looking paradigm (figure 5.6) and has a contrast range of 100% to 1.25% (i.e., 0.00 to 1.9 logCS) (table 5.4). In this study, single-sided Heidi cards were used to avoid examiner bias as much as possible.

The mean chart luminance was measured to be 98±11 cd/m^2. The PI presented the 'blank' card and the 'face' card with equal horizontal movement and the response of the child was observed. Only when the children's eye movements were not clear due to a high amplitude of the horizontal nystagmoid movements, the vertical movement of the cards was preferred. If the child did not look at the face card, the previous contrast card was presented to the child three times. The response obtained two out of three times was considered and the contrast was thresholded.

Figure 5.6: Contrast sensitivity testing using Hiding Heidi low contrast face test

(Note: Photo consent obtained from the parent)

Ohio contrast cards

In the current study, the horizontally oriented OCC were presented to the child at a distance of 55 cms. The median chart luminance was measured to be 80±7 cd/m^2. The contrast cards had square-wave grating at a very low spatial frequency of 0.15 cycles per degree and contrast varied from 100% to 2.2% (i.e., 0.00 to 1.66 logCS) (table 5.4) (figure 5.7). The descending method of limits was followed. The direction of the grating at each contrast level was randomly placed and the PI was masked to the direction of the gratings before presenting to the child in order to minimize the examiner bias. The child's response to the grating was noted as right/left in the data sheet. If the child had given a different response than the actual orientation of the grating, then that card was presented two more times and the response that was obtained two out of three times was considered. If the child was not/incorrectly responding to a particular card for two out of three times, then the card that was shown earlier was presented again for confirming and the response was noted. This was considered as the end point of the test. This additional step of showing the earlier card was only towards the thresholding of the contrast and for confirmation purposes.

Contrast sensitivity test	Test distances (cms)	Range of testable contrast sensitivity values (logCS)
Ohio contrast cards	55	0.00 to 1.66
Hiding Heidi	Not specified (50 cms used in this study)	0.00 to 1.9

Table 5.4: Contrast sensitivity tests with their test distances and range of testable contrast sensitivity values

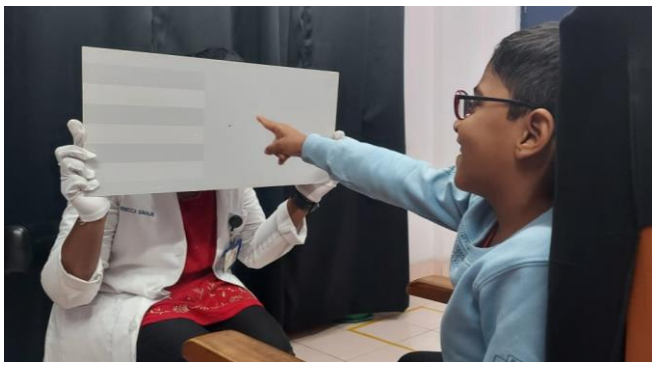


Figure 5.7: Contrast sensitivity testing using Ohio contrast cards

(Note: Photo consent obtained from the parent)

5.7 Procedure

Children who consulted in the neurology clinic at Rainbow Children's Hospital, Hyderabad with CVI formed the major cohort of participants in the study. The paediatric neurologist diagnosed the child to have CVI based on the history and neuroimaging findings. Referral to geneticist was considered in cases where neuroimaging findings were normal but the child was suspected to have CVI. After confirmation of the diagnosis, based on the age of the child (i.e., 6 months to 7 years), the neurologist (supervisor Dr. LL) considered referral for the study recruitment. As the study cohort was primarily recruited from the neurology clinic, a comprehensive eye evaluation could not be done on all the children, but referral was provided to all. The PI approached the parents/caregivers of the child and explained about the study using the participant information sheet. After checking their willingness to allow their child to participate in the study, the consent form was provided to the parents/caregivers to read through and consent as appropriate. In addition to English, the participant information sheet and the informed consent form was also available in Hindi and Telugu, i.e., the two most commonly spoken regional languages in the city in which the study was conducted (Demographics of Hyderabad, 2022). A separate informed consent was also

obtained for recording the video of the vision assessment that was later used for inter-examiner analysis. The PI filled in the data sheet with the information given by the parents/caregivers and by verifying the medical records. The data sheet contained information relating to demographic and clinical details such as: chronological age, gender, location and clinical data such as diagnosis, aetiology, associated features (such as: seizures, vaccination history), birth and developmental history (including developmental milestones), chief complaints (both overall and visual) *(see appendix (A10))* seizure history, rehabilitation therapies undertaken and treatment advised. Parental concerns about the functional vision concerns of the child were asked as an open-ended question, "What are the vision-related problems that you have noticed in your child?" without any specific leads or prompts to maintain consistency to elicit responses. All visual concerns that were reported by parents/caregivers were recorded. No structured questionnaire was used for collecting this information. The question was asked before the assessment procedures whenever possible in order to avoid any potential parental bias in reporting the visual concerns by observing the child's response to the visual assessment.

Some children were also recruited by the PI from the Special Needs Vision Clinic, Institute for Vision Rehabilitation at L V Prasad Eye Institute, Hyderabad, India (PI's primary workplace) and referred to the neurology clinic of Rainbow Children's Hospitals, Hyderabad for developmental screening assessment (using DDST-II), consulting neurologist and including electroencephalography (EEG) procedure based on the clinical judgement of the neurologist. Charges for the developmental screening assessment were funded as part of the study, as it is not regular clinical practice to assess developmental domains for all children with CVI. However, EEG and MRI are normally routine clinical diagnostic tests advised by the paediatric neurologist and these were not funded as part of the study.

High resolution pictures of the child's MRI films of the brain were taken and later analysed by the neuro-radiologist using the criteria (mentioned in table 5.2) that has been revised from the earlier established criteria (Cioni et al., 2000) (see section 1.5.2) and tested in this study based on the location and extent of damage. The PI took high-resolution pictures of the films (physical copies)[10] by placing them against a lightboard for good clarity. These pictures were later sent to the neuro-radiologist for grading purposes. Retrieving MRI films of all children was not possible, as the

[10] *In India, results of all the diagnostic tests are not mandatorily uploaded in the patient medical records and there is no central medical record as in UK*

parents/caregivers did not bring the MRI films on that particular visit to the neurologist's/ophthalmologist's clinic. Those parents were reminded to bring the films in the next visit (retest visit). Electroencephalography, similar to neuroimaging was not specifically performed for the purposes of the current study but was performed as per the clinical protocol followed by the Rainbow children's hospital in the neurology clinic for the management of some children with CVI. Based on the clinical judgement of the neurologist, which is primarily dependent on the complaints reported by parents/caregivers about seizures or deterioration in child's overall functioning or when silent seizures[11] were suspected, some children who participated in the study were advised to undergo EEG. It is important to record seizure activity as it can potentially play a role in the psychosocial functioning of the children (Marston et al., 1993) and any variation can potentially vary the overall development and visual function measurements as well. Electroencephalography was carried out by a single technician who was experienced in performing electrophysiological techniques in children with CVI to record brain activity for seizures.

The developmental quotient/age was determined by a child psychologist using the second version of the Denver Developmental Screening Test (DDST- II) (Frankenburg et al., 1992b). The description of the test is given in section 5.6.2 and the questionnaire is attached in the appendix (A13). The severity of CVI was graded by the PI with the assistance from an experienced vision rehabilitation professional (PE) using the CVI range developed by Roman-Lantzy that categorizes study participants into one of the 3 phases of CVI (phase 1: building visual behaviour, phase 2: integrating vision with function and phase 3: resolution of CVI characteristics). The following 10 characteristics were used: colour preference, need for movement, visual latency, visual field preferences, difficulty with visual complexity, light gazing and non-purposeful gaze, difficulty with distance viewing, atypical visual reflexes, difficulty with visual novelty and absence of visually guided reach (Roman-Lantzy, 2010).

Room illuminations ranged from 250-320 lux which was measured using HTC-luxmeter (LX-101A). The VA and CS tests were randomized. As described previously, the descending method of limits was followed for presenting VA and CS tests, except for PV where an automated staircase procedure was used. As part of the study protocol, before recruiting the first subject for the day, the room illumination was measured, calibration of the instruments and testing distance markings were checked to maintain consistency throughout. Maintaining the testing distance was ensured using the

[11] *unnoticed by parents/caregivers primarily when the child is asleep*

manually placed distance markings on the table. In case the child had moved closer, then the PI accordingly moved back in order to maintain the working distance. As the card length for TAC-II and OCC was 55 cms, the length of the card was also used for quick checking of the distance during the assessment. All the VA and CS assessments were carried out at the child's eye level.

As descending method of limits was used for the majority of the visual function tests (for all except for PV app), checking for the examiner bias if any is an important step. Video recording of the TAC-II procedure carried out by the PI was analysed in a random sample of children with CVI by an experienced second examiner (i.e., an optometrist with an experience of 4+ years in assessing and managing children with SEN), who was masked to the readings of the PI. The independent examiner was asked to judge the response of the child to the particular grating that was presented and document their decision on a separate data sheet. After studying the second examiner's decision based on the responses to all the gratings given by a particular child, the VA estimated was noted and compared against the PI's readings. Additionally, the examiner was asked if they completely agreed with the PI on the thresholding or if additional testing beyond the PI's threshold was required. These responses were analysed as well. On reflection it would have been appropriate for the PI to show at least one or two cards at a higher frequency after they felt threshold was achieved so that the independent examiner could judge the endpoint themselves. However, this was not carried out for the current study and we will discuss the limitations of our approach in the discussion.

The video was recorded using a camera (Canon EOS M50 24.1 mega pixels mirrorless camera with EF-M 15-45 (electro-focus mount) with STM (stepper motor) lens. The STM lens helps in eliminating noise during the video recording and allows for a smoother focus system (What does STM mean on a Canon lens? (Shuttermuse)). The camera has a horizontal display resolution of 4K (4096x2160) which is about 8.5 megapixels (Silva, 2021) . This was placed on a tripod stand and positioned behind the PI at a distance of 1 metre. In case the child was distracted due to the positioning of the camera (for e.g., if the child's attention was drawn to the camera instead of the visual function tests), the camera was placed accordingly to capture the child's responses and the overall behaviour during the visual functions testing process. The grading used for the engagement scores in Livingstone et al's study (Livingstone et al., 2019) was followed here. This was graded on a scale of 0-2 with 0 indicating 'no engagement', i.e., when there was no meaningful response that could be elicited due to poor engagement, 1 indicating 'partial engagement', i.e., some meaningful

response that could be elicited, but there was loss of child's interest before reaching upto convincing threshold and 2 indicating 'complete engagement', i.e., when the child's engagement was upto convincing threshold or finest grating or contrast presented.

Test-retest repeatability of VA and CS assessments were attempted at/within 2 weeks duration. However, only a few participants were able to come for the retest within 2 weeks duration and many were lost to follow-up as a result of the first and second wave of the pandemic. Therefore, the retest assessment was considered until 1 month of duration. The role of different professionals involved in the current study is summarized in table 5.5.

Control group: A control group consisting of chronologically age-similar typically developing children was recruited to have a comparative normative group. The pre-COVID proposal was to approach schools or similar organizations for recruitment of control subjects. However, due to COVID-19 restrictions, play schools and regular schools were functioning online and hence recruitment was not possible through the schools. The PI with the help of a local church organized a one-day vision screening camp for typically developing children in Hyderabad. As part of the screening program, age-similar controls were recruited. Further recruitment took place at a local church, at a local home for the homeless and by including normal siblings who accompany children with CVI to the hospital. The amendments for the new recruitment sites were approved by the ethics committee of LVPEI. The calibration measures of the instruments and illumination levels were strictly adhered to as mentioned earlier.

Both for test and retest assessment for cases and controls, the PI was completely masked to the location of the gratings for both TAC-II and OCC and picture in case of HH cards, as the cards where placed upside down. During video recording for assessing examiner bias, the PI oriented the gratings side of the card towards the camera placed left side of the PI. During the retest of the visual functions, the PI did not refer to the earlier data sheet to avoid bias.

Role of professionals in the current study						
Tests performed	**Principal investigator**	**Paediatric neurologist**	**Neuro-radiologist**	**Vision rehabilitation specialist**	**Clinical psychologist**	**Optometrist (examiner 2)**
Establishing the diagnosis of CVI						
Explaining the study protocol and obtaining informed consent						
Verifying medical records and eliciting relevant history						
Assessment of visual functions						
Functional vision assessment						
Grading of neuroimaging						
Developmental assessment						
Video analysis for interobserver analysis						

Table 5.5: The role of different professionals in the current study

The tests carried out in the current study are summarized in the flow chart (figure 5.8).

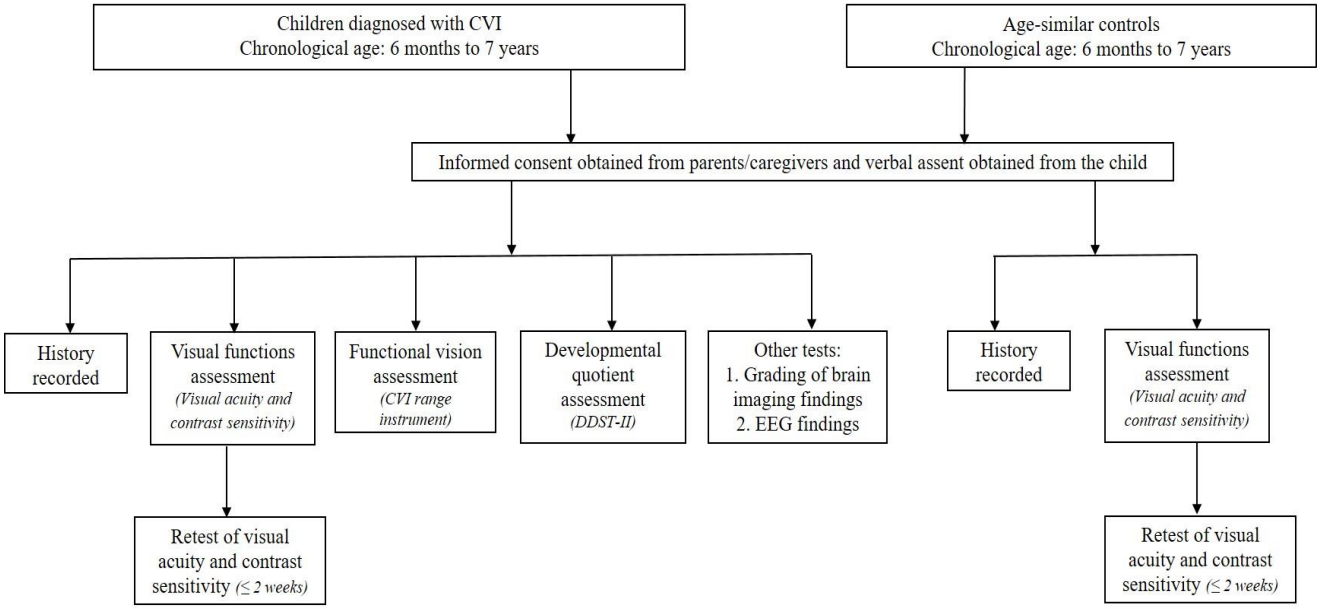


Figure 5.8: Flow-chart of the tests that were carried out as part of the study protocol for children with CVI and age-similar controls

(DDST-II: Denver Developmental Screening Test-II, EEG: Electroencephalography)

Timescales

The data collection phase for the study was initiated in October 2020, i.e., post first pandemic lockdown in India (complete lockdown in India was from March 25, 2020 to May 31, 2020) (figure 5.9). Permission was sought from Rainbow children's hospitals and at LVPEI, Hyderabad, India for initiating the data collection with precautionary measures in place. Most of the children were recruited during their waiting period at the neurology clinic. Parents were keen on spending less time in the hospital to avoid any potential exposure to the virus and therefore performing comprehensive eye examination for all the children proved challenging on the same day. Therefore comprehensive eye examinations were attempted only when the children could come for a retest. The overall number of the children attending Rainbow children's hospitals and LVPEI was reduced due to the consequences of the pandemic and this had an effect on achieving the calculated sample size.

The retest phase was also impacted by the second pandemic lockdown (partial lockdown in Telangana state was May 12, 2021 to June 19, 2021) (figure 5.9). Although the COVID restrictions had been lifted partially, some parents had reservations about bringing their children back to the clinic in a short time duration. As a result, the retest phase for some children took place beyond the initial 2-weeks.

Consequently, the study protocol was modified to accommodate a retest period of up to one month for eligible children.

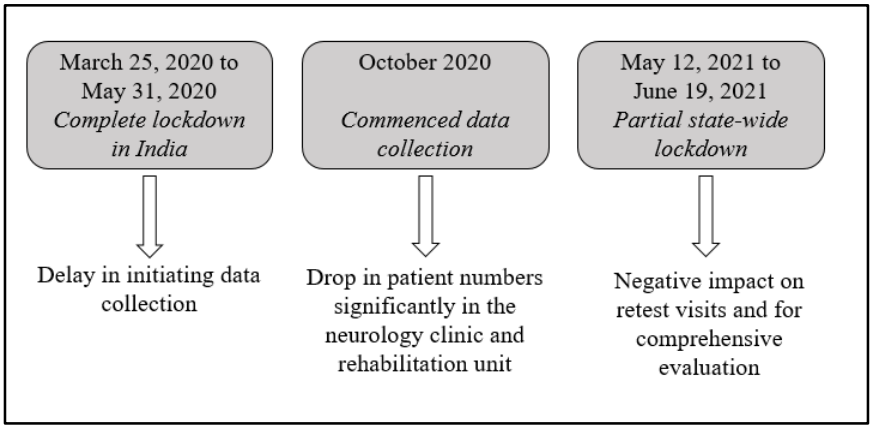


Figure 5.9: Impact of COVID-19 pandemic on data collection phase in the current study

5.8 Statistical analysis

As the data was not normally distributed, non-parametric statistical tests were chosen for analysis purposes. The data was entered on Microsoft excel-Office 365 (Microsoft Corporation, 2018) and final analysis was carried out using SPSS (ver. 20) (IBM Statistics for Windows, 2011). Demographic and clinical characteristics of the children were reported in percentages and the significance of the proportions were determined using the Chi-square test. The testing time and binocular presenting visual functions were analysed within children with CVI and controls using Wilcoxon-signed rank test. Between the group comparisons were performed using Mann-Whitney U test. The agreement of the visual function estimates was determined by mean differences, SD and 95% LoA. The repeatability of the visual functions was determined by using 95% LoA and coefficient of repeatability (CR). The DQ/DA, MRI grading, functional vision score and presence of seizures were reported using mean, SD and percentages. The relationship of secondary parameters such as: seizure episodes, functional vision score, MRI grading and DQ/DA were studied in relation to the visual functions in children with CVI using correlation coefficient (Spearman-rho test), coefficient of determination and by understanding across-the-phases differences using Kruskal-Wallis test.

Chapter 6 : Results

6.1 Chapter overview

This chapter describes the study findings of all the 5 objectives (mentioned in section 3.3 and 5.1). All the tests (as described in section 5.6) could not be carried out on all children with CVI due to limited cooperation from the child, limited available time as reported by parents/caregivers to complete the study-related tests and the consultation by the neurologist/ophthalmologist, inability to come another day due to travel concerns and due to partial lockdowns and restrictions imposed due to the pandemic. Figure 6.1 gives an overview of the children with CVI and controls who were enrolled in the study and also the data available for each parameter.

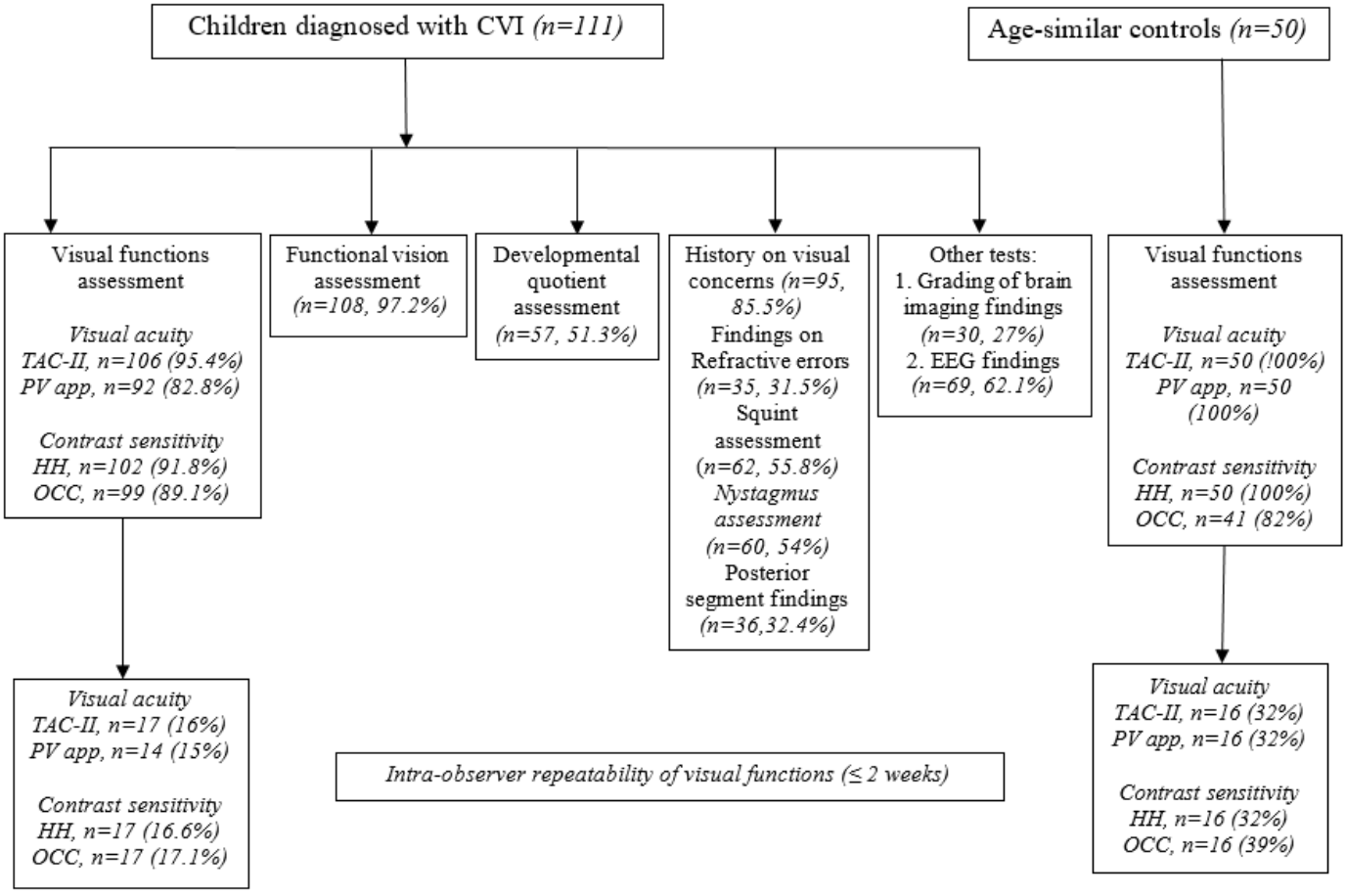


Figure 6.1: Overview of the available data of children with CVI and controls

(Note: The sample size under each category was different, as all tests could not be carried out on all children)

(TAC-II: Teller acuity cards-II, PV app: Peekaboo Vision app, HH: Hiding Heidi cards, OCC: Ohio contrast cards, EEG: electroencephalography)

6.2 Objective 1: Demographic and clinical characteristics of children with CVI and typically developing children

6.2.1 Basic demographic information

Children with CVI

A total of 111 children with CVI were recruited over a study period of Oct 2020-April 2022. A majority of the children (n=84, 75.6%) were recruited from the paediatric neurology clinic and others (n=27, 24.3%) were recruited from the Institute for Vision Rehabilitation at L V Prasad Eye Institute.[12] The mean age of the children was 3.00±1.85 years (range=7 months to 7 years, median: 2.5 years). The mean age of presentation to the paediatric neurology clinic was noted to be 2.81±1.88 years (n=81) as compared to that of the paediatric vision rehabilitation centre which was 3.46±1.63 (n=27), which was found to be significantly different (p=0.03, Mann Whitney). There was a significantly larger proportion of males (n=78, 70.2%) when compared to females (n=33, 29.8%) (p<0.001, Chi-square test). Data about where the children lived i.e., their permanent residential location was available for 103/111 children. A little over a third of the children (n=39, 35.1%) resided locally (i.e., in and around Hyderabad, Telangana, India), others (n=38, 34.2%) were from the state of Telangana (outside Hyderabad) or other states of India such as Maharashtra, Karnataka and West Bengal (n=25, 22.5%) and 1 child was from Kenya (0.9%) (table 6.1).

Control group

Age-similar typically developing controls (n=50) were recruited. Only those children whose parents/primary caregiver reported no vision concern were recruited in the control group. All the children were normal on torch light examination carried out by the PI with no obvious anterior segment abnormalities. The mean age of the children was 3.39±1.87 years (range: 7 months to 6.83 years, median: 3.0 years). There was no significant difference in the age of children with CVI and controls (p=0.17, Mann-Whitney test). There were a greater number of girls (n=31, 62%) when compared to the boys (n=19, 38%) (p=0.09) in the control group but were comparable based on their chronological age (p=0.44, Mann Whitney). A majority of controls were recruited from a local children's home (n=19, 38%) and from the local church community (n=19, 38%). A small percentage

[12] *LVPEI and Rainbow are tertiary hospitals that see patients from all over India and from other countries as well. Both the hospitals are based in the city of Hyderabad located in the state of Telangana*

of children were recruited in the clinics (Rainbow children's hospitals (n=1, 2%) and LVPEI (n=9, 18%)), which included children who had accompanied their siblings for an examination and children of staff. Two (4%) children were recruited at the residential complex of the PI. All the children were based in Hyderabad (n=50, 100%) (table 6.1).

Characteristic	CVI (n=111)	Controls (n=50)	p-value
Age			
Mean±SD (years)	3.00±1.85	3.39±1.87	0.17
Range	7 months to 7 years	6 months to 6.83 years	
Gender (n, %)			
Males	78 (70.2%)	19 (38%)	Children with CVI= <0.001 Controls=0.09
Females	33 (29.7%)	31 (62%)	
Place of recruitment (n, %)			
Rainbow children's hospitals	84 (75.67%)	1 (2%)	
LVPEI	27 (24.33%)	9 (18%)	
Residential area	-	2 (4%)	
Church	-	19 (38%)	
Children's home	-	19 (38%)	
Residential location (n, %)			
In and around Hyderabad	39 (35.13%)	50 (100%)	
Telangana (excluding Hyderabad)	38 (34.23%)	-	
Other Indian states	25 (22.52%)	-	
Outside India	1 (0.9%)	-	
Information not available	8 (7.2%)	-	

Table 6.1: Basic demographic information of children recruited in the study (CVI, n=111) and (controls, n=50)

6.2.2 Clinical characteristics of the CVI cohort[13]

Aetiologies of CVI

The aetiology of CVI was available for 105/111 (94.5%) children. Neonatal hypoglycaemic brain injury was noted to be the most common aetiology in this cohort (n=50, 47.6%). The other causes included: Hypoxic Ischemic Encephalopathy (HIE) (n=26, 24.7%), Periventricular leucomalacia (PVL) (n=8, 7.6%), genetic causes (n=9, 8.5%) trauma (n=2, 1.9%), infection (n=9, 8.5%) and perinatal stroke (n=1, 0.9%).

[13] *The available data for each parameter is included along with percentage. For example, available in (45/111 children, 40.5%).*

Birth and family history

The mean gestational age was 35.61±3.06 weeks with a range of 24.0 to 40.0 weeks (89/111, 80.1%). The mean birth weight was noted to be 2.45±0.73 kgs with a range of 0.75 to 4.2 kgs (93/111, 83.7%). A majority of deliveries were through caesarean section (n=67, 72.82%) when compared to the vaginal route (n=25, 27.17%) as reported by 92 parents/caregivers (82.8%). One child was conceived through in-vitro fertilization (IVF). A majority of the parents/caregivers reported that the child cried immediately upon birth (n=64, 75.29%) (85/111, 76.5%). APGAR scores were not reported by any of the parents/caregivers as they were not aware of the scores.

A total of 78/111 (70.2%) were asked about a history of consanguinity, 14 parents (17.94%) had consanguineous marriages. The mean age of the mothers at the time of the delivery was recorded to be 27.12±4.81 years (range: 18.0 to 39.0 years) (64/111, 57.6%). A majority (n=53/79, 67.1%) of the children were the first child of their parents (79/111, 71.1%). Only 1 child's sibling (3.3%) was affected with similar visual and developmental concerns as reported by the parents (30/111, 27%).

Neonatal jaundice was reported in 33/86 children (38.3%), whereas neonatal pneumonia was reported only in 7/82 children (8.5%). Maternal complications were reported in 30/84 (35.7%) mothers. The antenatal complications included: hypertension=14, 46.6%; fever= 6, 20%; thyroid abnormalities= 3, 10%; gestational diabetes=2, 6.6%; anemia= 1, 3.3%; COVID-19= 1, 3.3%; ovarian cyst=1, 3.3%; ectopic pregnancy=1, 3.3%. In one case (3.3%), multiple pregnancy related complications led to the mother's death immediately after the delivery.

Medical history

History of additional neurological conditions were documented in 43/111 children (38.7%) (table 6.2).

Additional neurological conditions	Results (n=43)
Static encephalopathy	19 (44.1%)
Remote symptomatic epilepsy	15 (34.8%)
Occipital plagiocephaly	3 (6.9%)
Cystic encephalomalacia	1 (2.3%)
Acute necrotizing encephalopathy	1 (2.3%)
Secondary startle syndrome	1 (2.3%)
Obstructive hydrocephalus	1 (2.3%)
Joubert syndrome	1 (2.3%)
Klipell-Feil syndrome	1 (2.3%)

Table 6.2: Additional neurological conditions in children with CVI (n=43)

Seizures

Seizures were reported by the parents/caregivers in a large proportion of children (87/111, 78.3%). The type of seizure was documented in the medical records in 84 children (96.5%). The most common type was epileptic seizures in 70 children (83.3%) followed by infantile spasms noted in 14 children (16.6%). Information about the frequency of the seizure episode was available for 80 children (72.1%) (table 6.3).

Seizure episode	Results (n=80)
On daily basis	16 (20%)
Within last week	4 (5%)
Within last month	9 (11.2%)
Between over a month to 3 months	2 (2.5%)
Between over 3 months to 6 months	6 (7.5%)
More than 6 months	23 (28.7%)
Only at the time of birth or within 1 week of birth	11 (13.7%)
Not sure	9 (11.2%)

Table 6.3: Frequency of seizure episode in children with CVI (n=80)

Medication and other treatments

Seventy-four children had been advised a combination of medications for several reasons: antiepileptic medication was noted in 71 children (95.9%), steroid usage was documented in 11 children (14.8%), medication for enhancing cognition skills and for attention issues was documented in 19 children (25.6%), medications for muscle stiffness was being used in 3 children (4.1%) and for stroke in 3 children (4.1%).

History about stem cell therapy was available only in 45/111 children. Only 2 children had previously undergone stem cell therapy (4.44%). 1 child 2 years ago and the other child 3 months ago. History about vitamin-B12 usage was available in 44 children, of which 15 had used this previously on advice of their doctor (34.1%).[14]

Rehabilitation history

A small percentage of parents/caregivers reported that their child underwent home-based rehabilitation therapies (8.1%, 9/111), out of which 4 (44.4%) of them availed all the therapies, i.e., vision, speech, physiotherapy and special education by a professional therapist. Home-based vision therapies were carried out by parents/caregivers as follows: vision therapy, n=3 (33.3%); physiotherapy, n=2 (22.2%) and speech therapy, n=1 (11.1%). The most common reasons as reported by the parents/caregivers for not seeking help from professionals for early intervention therapies included lack of professional therapists locally, travel concerns and seizure episodes taking priority. However, all parents were counselled as part of this study to avail early intervention therapies by the PI *(the PI has clinical experience in the vision assessment and management of children with SEN).* For children with frequent history of seizures, the PI consulted the paediatric neurologist (supervisor Dr. LL) before suggesting early intervention therapies.

Parents' presenting concerns (developmental and visual)

Developmental concerns

Overall developmental concerns included perceived delay in all developmental milestones i.e., vision, motor, speech and cognition. This was reported in a majority of children (n=81/111, 72.9%). Isolated concerns or a combination of any two developmental concerns were reported in 13 children (11.7%) such as: only vision, n=5; only cognition, n=1; vision and speech, n=1; speech and cognition, n=1 and

[14] *Both the questions were introduced mid-way in the study as advised by the neurologist (supervisor Dr. LL) as few parents reported an improvement in the child's overall development post stem cell therapy/vitamin B12 usage.*

vision and motor, n=5. Specific motor concerns were reported in 76 children (68.4%), speech in 69 (62.1%) and cognitive concerns in 78 (70.2%) children. Auditory concern was reported only in 1 child (0.9%) (table 6.4).

Developmental area	Result (n=111)
Motor (n=76, 68.4%)	
Overall delay	44
Neck holding concerns	13
Unable to crawl	4
Unable to sit	2
Unable to walk	17
Unable to reach out to objects	5
One-sided restriction (hemiparesis)	5
Speech (n=69, 62.1%)	
Overall delay	46
Slurred speech	7
Only bi-syllables	6
Only few words	10
Cognition (n=78, 70.2%)	
Attention	2
Lack of socialization	2
Behavioural issues	8
Cognitive delay	68
Auditory (n=1, 0.9%)	1

Table 6.4: Classification of developmental concerns (n=111)
(Note: A few parents reported more than one specific concern in each area)

Visual concerns[15]

Parent-reported visual concerns were available in 95/111 (85.5%) children. Interestingly, no visual concerns were noted in 6 children (6.3%). A single concern only was reported in 61 children (64.2%) and two visual concerns were reported in 28 children (29.4%). The two most common visual concerns included difficulty in recognizing faces (32.6%) and in maintaining eye contact (30.5%) (figure 6.2).

[15] *Article published in the Journal of Clinical Optometry in July 2023 (see Appendix A15)*

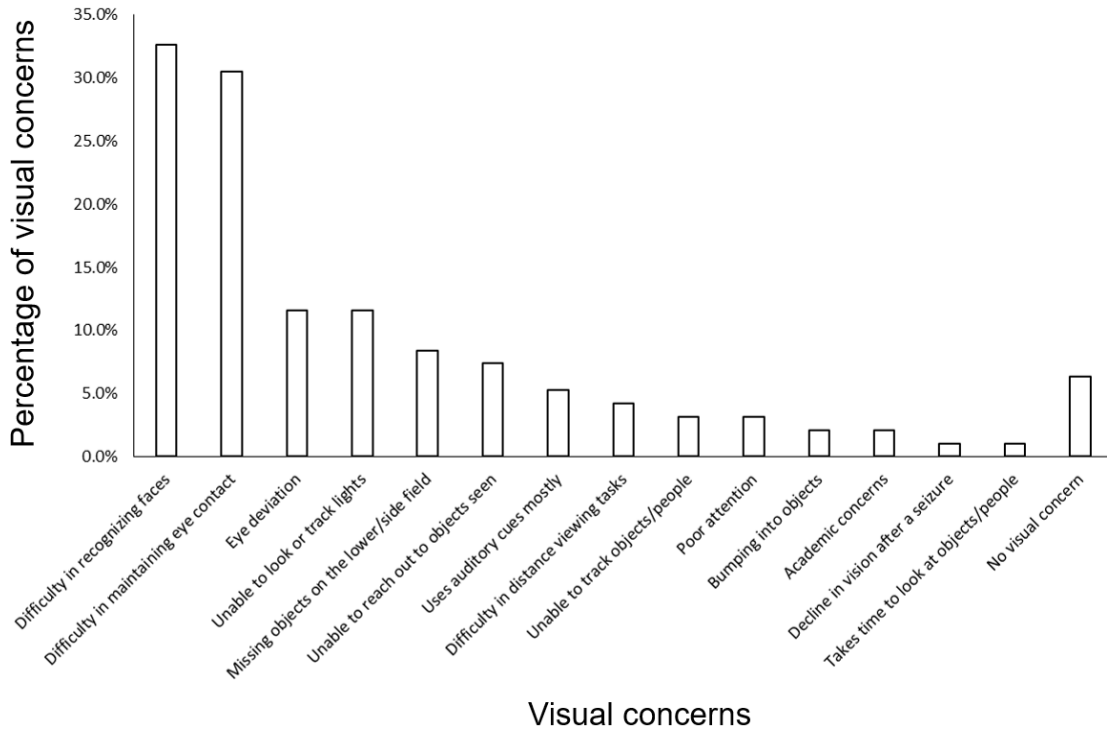


Figure 6.2: Bar graph representing the frequency distribution of visual concerns reported by parents (n=95)

(Note: Visual concerns are greater in number than the sample, as some parents (n=28) reported more than one visual concern)

Children were divided into 3 categories based on their chronological age (6 months to 1 year, n=13; >1 year to 3 years, n=42 and > 3 years, n=40) (figure 6.3). The frequency distribution of all visual concerns (including 'no visual concerns, n=6) was found to be comparable across all 3 age categories (p=0.66, Pearson chi-square). Difficulty in recognizing faces (6 months to 1 year, n=7, 53.8%; >1 to 3 years, n=18, 42.9%) and maintaining eye contact (6 months to 1 year, n=4, 30.8%; >1 to 3 years, n=15, 35.7%) were noted to be the top two concerns in these age categories. In children above 3 years of age, difficulty in maintaining eye contact remained as a major visual concern (n=10, 25%) followed by missing objects on the lower/side field (n=7, 17.5%). More than 1 visual concern was reported at a greater frequency among the >1 to 3 years age category (50%), followed by >3 years age category (35.7%).

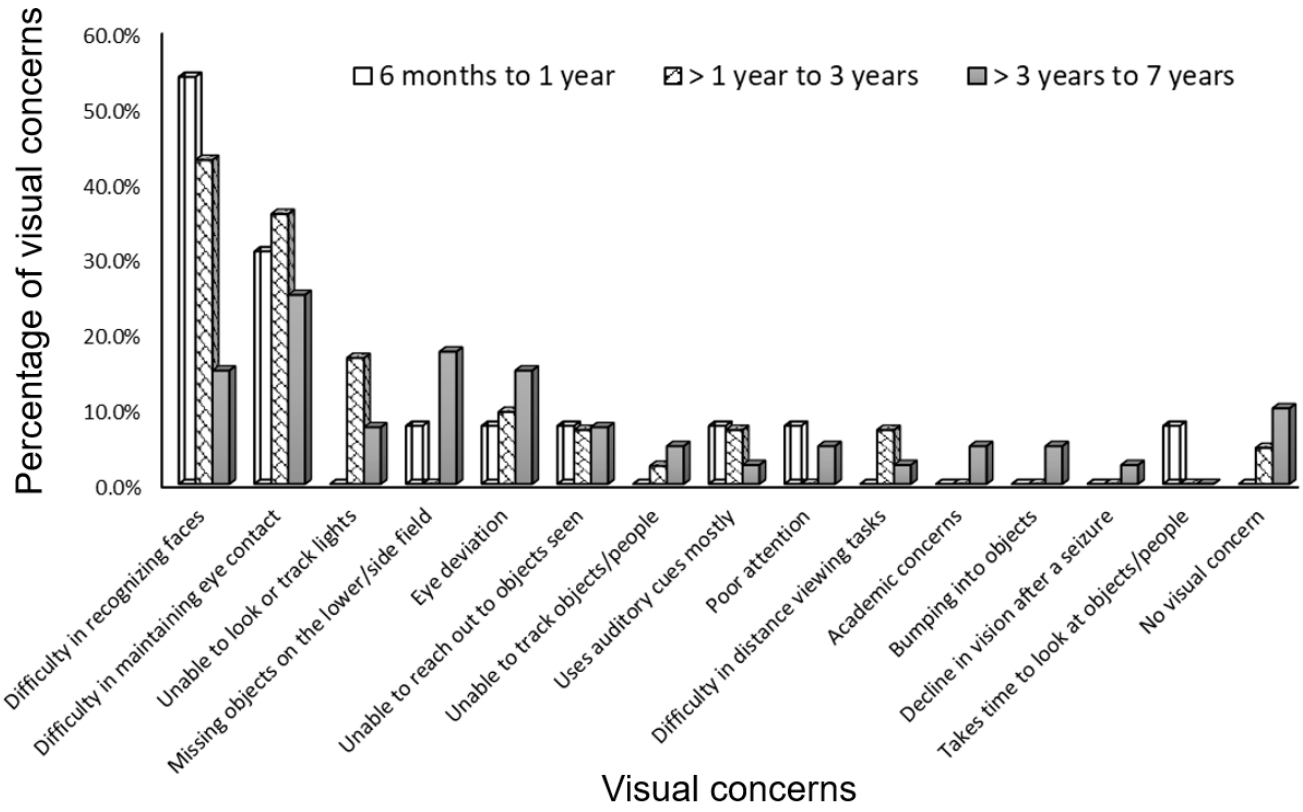


Figure 6.3: Clustered bar graph representing the frequency distribution of visual concerns reported by parents based on age categories (n=95)

(Note: Visual concerns are more in number than the sample, as some parents (n=28) reported more than one visual concern)

Other clinical tests

Refractive correction and eye health assessment

It was not feasible to perform a comprehensive eye evaluation on all the children with CVI, although this would have been ideal. However, all the parents/caregivers of children with CVI recruited at the neurology clinic at Rainbow children's hospitals were referred for a comprehensive eye evaluation at LVPEI *(PI's workplace).* Unfortunately, there was reduced uptake for the eye examination by the parents/caregivers due to the following reasons: seizure control being the chief concern, travel concerns to report to the eye clinic despite the clinic being less than a mile away (however, only 1/3rd of the cohort resided within Hyderabad city (n=39, 35.1%)), difficulty in accommodating both neurology and eye examination appointments on the same day and some parents did not prefer to visit the hospital another day due to the pandemic. Therefore, refractive correction (35/111) and eye health

assessment details (36/111) were only available in one-third of children with CVI. The remaining parents were counseled to organize an eye examination for their child at a later date or close to where they lived.

Refractive errors were present in all 35 children on whom refraction was performed (100%) (table 6.5). Refraction could not be carried out on one child as the child was restless during the examination and was advised to visit on another day for comprehensive evaluation. However, due to travel constraints, the patient could not visit for a comprehensive evaluation. Surprisingly, only 4 children (3.6%) had a history of using spectacles and were using them during the recruitment. Mixed astigmatism was noted to be the most common type of refractive error (37.1%), followed by compound hyperopic astigmatism (20%). Fourteen children (40%) were prescribed spectacles based on the American Academy of Ophthalmology - Preferred Practice Pattern guidelines. (Hutchinson et al., 2022) including those with ≥+3.00D considering that this value could be a visually significant refractive error in children with developmental delays (Pehere et al., 2018). However, all the children identified to have refractive errors were advised regular follow-ups as part of the regular clinical protocol for monitoring purposes. Measuringamplitude of accommodation using dynamic retinoscopy was attempted and could be recorded only in 4 children. Out of them 2 had a lag of accommodation >0.75D.

Type of refractive correction	**Results (n, %)**
Mixed astigmatism	13 (37.1%)
Compound hyperopic astigmatism	7 (20%)
Simple hyperopic astigmatism	4 (11.4%)
Simple hyperopia	3 (8.5%)
Compound myopic astigmatism	5 (14.2%)
Simple myopic astigmatism	1 (2.8%)
Simple myopia	2 (5.7%)

Table 6.5: Distribution of refractive errors in children with CVI (n=35)

Anterior segment evaluation was carried out using torch light examination and was noted to be within normal limits in all the 111 children. Among those children on whom other tests could be performed, optic atrophy was noted in 72.2% (26/36) (table 6.6), diagnosis of delayed visual maturation was made in

8.3% (3/36), squint was noted in 85.4% (53/62) (table 6.7) and nystagmus in 23.3% (14/60) children. Refraction and dilated examination could be attempted in only those children who could come for a comprehensive examination on another day (n=36). However, simple torch light examination was carried out on children to grossly assess for squint (n=62) and nystagmus (n=60) on the same day after assessing VA and CS, whenever possible.

Posterior segment finding	Results (n, %)
Optic atrophy	26 (72.2%)
Within normal limits	6 (16.6%)
Retinopathy of prematurity	1 (2.7%)

Table 6.6: Distribution of posterior segment findings in children with CVI (n=33)

Type of squint	Results (n, %)
Alternating exotropia	16 (25.8%)
Exotropia	15 (24.1%)
Esotropia	14 (22.5%)
Orthotropia	9 (14.5%)
Alternating esotropia	7 (11.2%)
Intermittent esotropia	1 (1.6%)

Table 6.7: Distribution of types of squint in children with CVI (n=62)

Electroencephalography

Electroencephalography findings were available for 69/111 children (62.1%) and abnormal EEG was noted in 54 children (78.2%). Based on the EEG report, in the background classification (n=39): generalized abnormalities were noted in 25 (64.1%) and focal in 14 (35.9%) children. Epileptiform discharges were found to be (n=38): focal in 11 children (28.9%), multifocal in 15 children (39.4%) and generalized in 12 children (31.5%). Laterality was documented in 18 children (bilateral, n=9 (50%) and unilateral, n=9 (50%)). Hypsarrhythmia was noted in 13 (24.1%) and epileptic encephalopathy in 36 children (66.6%). Sleep spindles were documented only in 8 children and were found to be absent in 4 children (50%) (table 6.8). In one EEG record, only intermittent slowing was noted with normal background and sleep spindles.

Classification	Findings (n=54)
Background (n=39)	
Generalized	25 (64.1%)
Focal	14 (35.9%)
Epileptiform discharges (n=38)	
Focal	11 (28.94%)
Multifocal	15 (39.47%)
Generalized	12 (31.5%)
Laterality (n=18)	
Bilateral	9 (50%)
Unilateral	9 (50%)
Hypsarrhythmia	13 (24.1%)
Epileptic encephalopathy	36 (66.6%)
Sleep spindles (n=8)	
Present	4 (50%)
Absent	4 (50%)

Table 6.8: Electroencephalography findings in children with CVI (n=54)

Neuroimaging

The MRI films were available in 30/111 children (27%) and were graded by a neuro-radiologist based on the criteria discussed in section 5.6.1. In one child, the white matter signal, occipital lobe/visual cortex and optic radiations could not be graded due to poor resolution of the images. A majority of the children were categorized into the moderate to severe grade (n=19, 63.3%), followed by the mild grade (n=10, 30.3%). Only 1 child was categorized into the normal grade (3.3%). The scoring of each parameter has been given in table 6.2.9. In the moderate to severe category, the most damaged location included the optic radiations (82.8%), followed by white matter signal (79.3%). The other moderate to severely affected locations included the occipital lobe/visual cortex (69%) and white matter reduction (66.7%).

Location of the damage/abnormality	Grade 1 (Normal) (n)	Grade 2 (Mild) (n)	Grade 3 (Moderate to severe) (n)
Size of lateral damage	7 (23.3%)	10 (33.3%)	13 (43.3%)
White matter signal	6 (20.7%)	-	23 (79.3%)
White matter reduction	9 (30%)	1 (3.3%)	20 (66.7%)
Cysts	24 (80%)	-	6 (20%)
Corpus callosum thinning	10 (33.3%)	12 (40%)	8 (26.7%)
Cortical matter (other than visual cortex)	17 (56.7%)	-	13 (43.3%)
Thalamus	24 (80%)	-	6 (20%)
Optic radiations	5 (17.2%)	-	24 (82.8%)
Occipital lobe/visual cortex	9 (31%)	-	20 (69%)

Table 6.9: Distribution of severity of the damage based on the location graded using the brain imaging findings (n=30)

Key findings

- Higher prevalence of CVI noted in boys (~70%)
- Common aetiology of CVI: NHBI (~50%)
- Approximately 80% of children with CVI had seizures
- Difficulty in recognizing faces (32.6%) and maintaining eye contact (30.5%) were the most commonly reported visual concerns
- Approximately 65% of children with CVI had moderate to severe brain damage
- Reduced uptake of comprehensive eye health assessment despite referral (33.3%)

Among those who had an ocular evaluation with CVI:

- Approximately 40% of children from available data (n=35) had refractive errors that were beyond age norms
- Approximately 50% from available data (n=62) had exotropia (~25% alternating and ~25% constant)

6.3 Objective 2: Validation of clinical tools to assess visual acuity in children with CVI and typically developing children

6.3.1 Testability, testing time, engagement score and order of testing for tests of visual acuity

a. Children with CVI

Visual acuity testability rates were found to be the highest with TAC-II (n=106, 95.4%) when compared to PV app (n=92, 82.8%) and 87 children (78.3%) were testable using both the VA tests . This indicates that 19 children were testable only using TAC-II and not using PV app, while 5 children were only testable using PV app and not using TAC-II. The testing time was found to be comparable using both TAC-II and PV app (p-value=0.8, Wilcoxon signed rank test) (table 6.10). Peekaboo Vision app was carried out as the first test in 54 children (62%), whereas TAC-II was carried out as the first test in 33 children (37.9%) (table 6.12). The reason for this unequal distribution for the order of testing was due to the poor cooperation by a few children (n=10), who were crying at the start of the examination and were pacified when presented with an electronic display (PV app) in place of the card-based test (TAC-II). The order of testing is only documented for children on whom both the VA tests were testable. This indicates that in case the child is testable using one tool and not testable using the other, this would be apparent in the testability rate but not in the order of testing.

Test	**CVI (n=111)**		**Controls (n=50)**	
	Testability (%)	**Testing time (mins)**	**Testability (%)**	**Testing time (mins)**
TAC-II	106 (95.4%)	2.23±1.17	50 (100%)	1.44±0.64
Peekaboo Vision	92 (82.8%)	2.24±0.98	50 (100%)	1.23±0.51

Table 6.10: Testability and testing time of tests of visual acuity in children with CVI (n=111) and in controls (n=50)

The engagement scores graded on a scale of 0-2 with 0 indicating ‘no engagement’, 1 indicating ‘partial engagement’ and 2 indicating ‘complete engagement’ (Livingstone et al., 2019) are listed below in table 6.11. Children who were not testable were not given an engagement score. A majority of the children were noted to have some meaningful to convincing results using both tests. These scores are provided by the examiner (PI). The chronological age was significantly different across the 3 different levels of engagement for TAC-II (p=0.02, Kruskall-Wallis). There was no significant difference between ‘no vs. partial engagement’ groups (p=0.71, Mann Whitney) and between ‘no vs.

complete engagement' groups (p=0.06, Mann Whitney). However, significant difference in chronological age was noted for 'partial vs. complete engagement' (p=0.006, Mann Whitney). Children in the 'complete engagement' group (mean=3.79±1.94 years) were found to be older than those in 'partial engagement group' (mean=2.62±1.61 years).

When the PV app was used, only 47/79 children (59.4%) were able to register a response by touching the screen themselves and for the remainder of the children (n=32, 40.5%) the PI clicked on the screen based on the eye movements of the child. There were significant differences in chronological ages across all the 3 groups based on the engagement levels (p=0.001, Kruskall-Wallis). On individual comparisons, there was no significant difference noted in the 'no vs. partial engagement' group (p=0.19, Mann Whitney). However, there was a significant difference between 'no vs. complete engagement' (p=0.001) and 'partial vs. complete engagement' group (p=0.003, Mann Whitney). Children in the 'complete engagement' group (mean=4.18±1.86 years) were found to be older than the 'no engagement group' (mean=2.39±1.72 years) and the 'partial engagement group' (mean=2.79±1.66 years).

CVI				**Controls**			
Test	**Score 0** ***(No engagement)***	**Score 1** ***(Partial engagement)***	**Score 2** ***(Complete engagement)***	**Test**	**Score 0** ***(No engagement)***	**Score 1** ***(Partial engagement)***	**Score 2** ***(Complete engagement)***
TAC-II (n=106)	11 (10.3%)	63 (59.4%)	32 (30.1%)	TAC-II (n=50)	0 (0%)	5 (10%)	45(90%)
Peekaboo Vision (n=92)	17 (18.4%)	50 (54.3%)	25 (27.1%)	Peekaboo Vision (n=50)	0 (0%)	5 (10%)	45 (90%)

Table 6.11: Engagement scores for TAC-II and Peekaboo Vision app in children with CVI and in controls

Parents/caregivers reported that the child would be happy to perform the test again if required using TAC-II in 84 children (79.2%) and using PV app in 70 children (76%). No fatigue/boredom was noted in 83 children (78.3%) using TAC-II when compared to 71 children (77.1%) using PV app based on parental feedback.

The effect of the order of testing on engagement score was found to be significant using the PV app (p=0.02, Chi-square) and not significant in the case of TAC-II (p=0.21) (table 6.12). Only 2 children (3.7%) were noted to be in the 'no engagement' group when TAC-II was the second test in order and 8 children (24.2%) with PV app as the second test in order.

Engagement score	TAC-II (first test) (n=33)	TAC-II (second test) (n=54)	Peekaboo Vision (first test) (n=54)	Peekaboo Vision (second test) (n=33)
Score 0 *(No engagement)*	2 (6.1%)	2 (3.7%)	4 (7.4%)	8 (24.2%)
Score 1 *(Partial engagement)*	23 (69.6%)	29 (53.7%)	30 (55.5%)	20 (60.6%)
Score 2 *(Complete engagement)*	8 (24.2%)	23 (42.5%)	20 (37%)	5 (15.1%)

Table 6.12: Order of testing categorised based on the engagement ratios in children with CVI (n=87)

b. Controls

Visual acuity testability rates were found to be comparable between TAC-II and PV app (100%). The testing time was found to be significantly faster with PV app when compared to TAC-II (p-value: 0.04) (table 6.10). The testing time per card for TAC-II was noted to be significantly faster (~4.75 times) for controls (mean=0.12±0.07 min) when compared to children with CVI (mean=0.57±0.49 min) ($p<0.001$).

The engagement score was found to be high, i.e., to convincing threshold or to the finest grating possible in 45 children (90%) with TAC-II and PV app (table 6.11). When PV app was used, all children could do the test, except for infants (6-9 months of age, n=3), for whom the PI clicked the screen based on eye movements of the child.

6.3.2 Visual acuity comparisons

a. Children with CVI

The mean visual acuity recorded with TAC-II was 1.46±0.64 logMAR (range: 0.19 to 2.3 logMAR) and with PV app was 1.05±0.68 logMAR (range: -0.18 to 2.20 logMAR). The mean difference (PV app – TAC-II) was noted to be -0.25±0.40 logMAR and this was noted to be significantly different (p-value: < 0.01) with 95% LoA: -1.03 to 0.53 logMAR (figure 6.4 a) (n=78). The quantifiable acuities using both VA tests was possible only in 78 out of 87 children (89.6%) using both tests. The comparison of the acuities could not be carried out on children who were 'not appreciating demonstration grating' on either test.

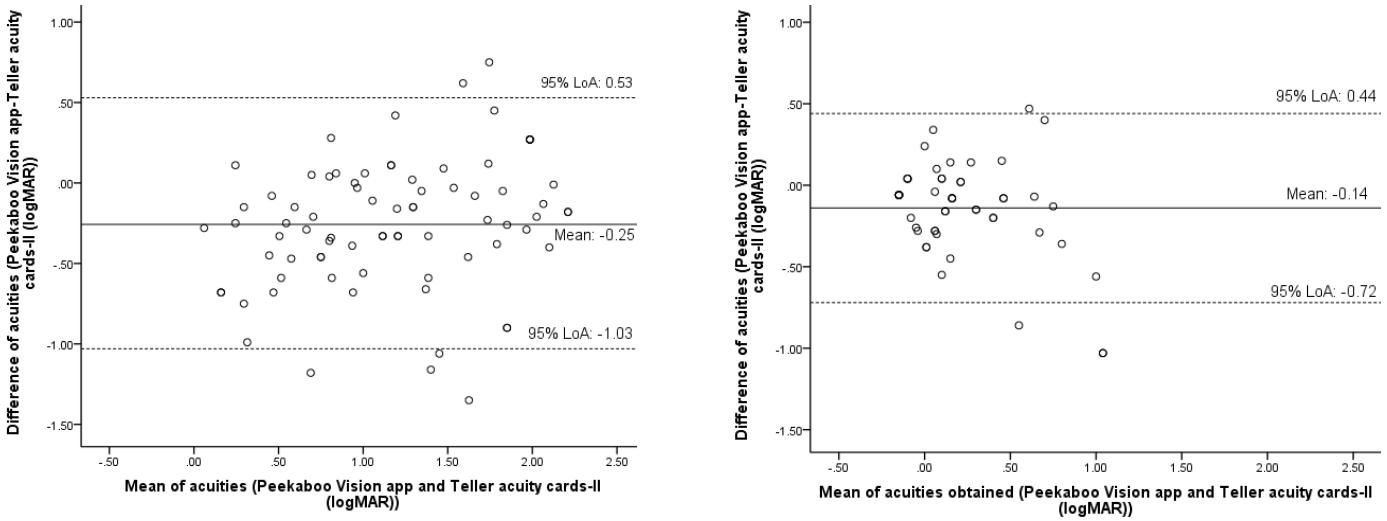


Figure 6.4: Bland-Altman plots of agreement between Peekaboo Vision app and Teller acuity cards-II in children with CVI (n=78) (a) and in controls (n=50) (b)

The mean acuities with the tests and their ranges have been summarized in table 6.13.

	CVI			**Controls**	
Test	**Mean±SD (logMAR)**	**Range (logMAR)**	**Test**	**Mean±SD (logMAR)**	**Range (logMAR)**
TAC-II (n=98)	1.46±0.64	0.19 to 2.30	TAC-II (n=50)	0.3±0.40	-0.12 to 1.55
Peekaboo Vision app (n=80)	1.05±0.68	-0.18 to 2.20	Peekaboo Vision app (n=50)	0.16±0.30	-0.18 to 0.90

Table 6.13: Mean and range of acuities obtained using TAC-II and Peekaboo Vision app in children with CVI and in controls (logMAR)

The mean difference and LoA between TAC-II and PV was determined for children with CVI only in the 'complete engagement' group separately (n=21). The mean difference between TAC-II and PV was noted to be -0.26±0.32 logMAR and it was noted to be significantly different (p=0.002, Wilcoxon) but with a narrower 95% LoA i.e., -0.88 to 0.36 logMAR.

b. Controls

The mean visual acuity recorded with TAC-II was 0.3±0.4 logMAR (range: -0.12 to 1.55 logMAR) and with PV app was 0.16±0.3 logMAR (range: -0.18 to 0.9 logMAR). The mean difference between the tests (PV app-TAC-II) was noted to be -0.14±0.30 logMAR (95% LoA: -0.72 to 0.44 logMAR, $p<0.001$) (figure 6.4b). The mean acuities with the tests and their ranges have been summarized in table 6.13.

The mean differences and 95% LoA between TAC-II and PV based on 4 different chronological age categories is summarized in table 6.14 for children with CVI and controls.

Children with CVI (n=78)			**Controls (n=50)**		
Age categories	**Mean difference±SD (logMAR)**	**95% LoA (logMAR)**	**Age categories**	**Mean difference ±SD (logMAR)**	**95% LoA (logMAR)**
6 months to 1 year (n=9)	-0.02±0.34	-0.68 to 0.64	6 months to 1 year (n=4)	-0.38±0.21	-0.79 to 0.03
> 1 year to 3 years (n=33)	-0.21±0.42	-1.03 to 0.61	> 1 year to 3 years (n=23)	-0.12±0.32	-0.74 to 0.5
> 3 years to 5 years (n=22)	-0.19±0.31	-0.79 to 0.41	> 3 years to 5 years (n=12)	-0.08±0.22	-0.51 to 0.35
> 5 years to 7 years (n=14)	-0.57±0.35	-1.25 to 0.11	> 5 years to 7 years (n=11)	-0.08±0.13	-0.33 to 0.17

Table 6.14: Mean differences and 95% limits of agreement for Peekaboo Vision app and TAC-II based on chronological age categories for children with CVI (n=78) and controls (n=50)

The 95% prediction limits of VA obtained using TAC-II from Leone et al's study (Leone et al., 2014) was used as a reference to plot against the acuity values of children with CVI and controls measured in the current study (figure 6.5). This was to double check that the controls fell within the 95% prediction limits, as they did not undergo complete eye examination, which would have been the ideal protocol to follow. Most of the data points from the current study were within the 95% prediction limits. However, a small number of children's acuity was worse than the lower limit (n=5 (10%), 6 months to 1.83 years of chronological age), likely due to poor concentration, this was apparent as their acuities using PV app were within the 95% prediction limits. A small number of children had acuity that was better than the upper limit (n=5, 10%, 3.66 to 7 years of chronological age) of the prediction limits. In children with CVI, only 18 children (18.3%, 7 months to 7 years of chronological age) were within the 95% prediction limits of typically developing children as reported by Leone et al (Leone et al., 2014).

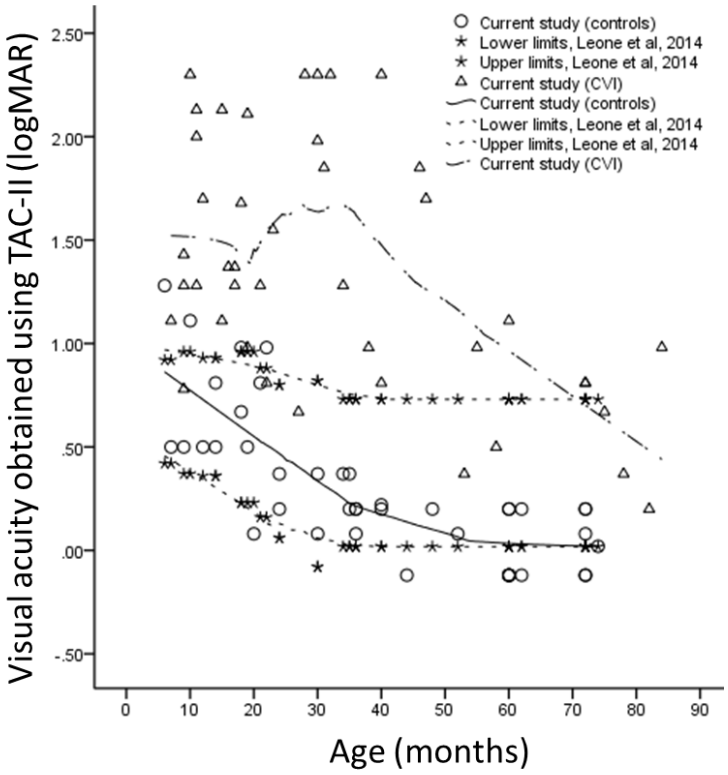


Figure 6.5: Scatter plot representing the visual acuity distribution obtained using TAC-II in typically developing (n=50) and in children with CVI (n=98) in this study along with 95% prediction limits of typically developing children from Leone et al's study

Assessing examiner bias

Examiner bias was assessed through the video analysis by a second examiner in a random sample of 30 children. The mean acuity differences between the estimates of PI and second examiner was noted to be 0.01±0.07 logMAR and 95% LoA: -0.13 to 0.15 logMAR with CR of 0.12 (figure 6.6).

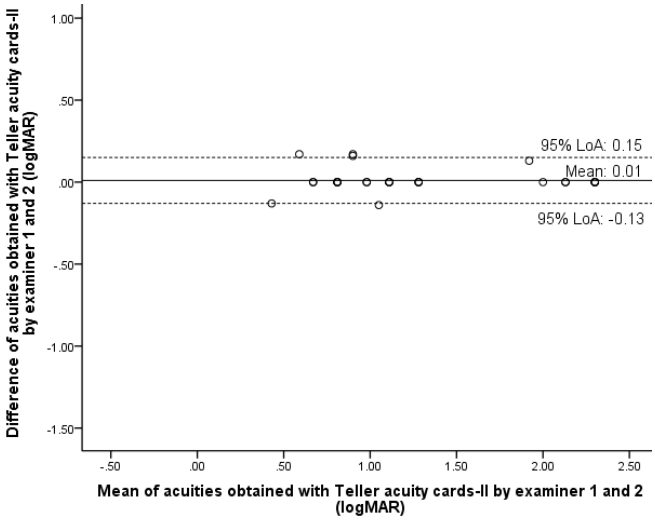


Figure 6.6: Bland-Altman plot of agreement of acuities obtained with Teller acuity cards-II by examiner 1 and 2 (logMAR)

Key findings		
Parameter	**CVI**	**Controls**
Testability	Higher with TAC-II (95.4%)	Comparable between TAC-II and PV app (100%)
"Complete" engagement score	Higher with TAC-II (30.1%)	Comparable between TAC-II and PV app (90%)
Testing time	Comparable between TAC-II (2.23±1.17 minutes) and PV app (2.24±0.98 minutes)	Shorter with PV app (1.23±0.51 minutes)
Mean difference between PV app and TAC-II	-0.25±0.40 logMAR	-0.14±0.30 logMAR
95% LoA between PV app and TAC-II	-1.03 to 0.53 logMAR	-0.72 to 0.44 logMAR
Peekaboo Vision app over-estimated acuity by 0.25 logMAR in children with CVI and 0.14 logMAR in controls when compared to TAC-II		

6.4 Objective 3: Validation of clinical tools to assess contrast sensitivity in children with CVI and typically developing children

6.4.1 Testability, testing time, engagement score and order of testing for tests of contrast sensitivity

a. Children with CVI

Contrast sensitivity testability rates were found to be marginally higher with HH cards (91.8%) than when compared to OCC (89.1%). The testing time was found to be significantly faster using HH cards when compared to OCC ($p<0.01$, Wilcoxon signed rank test). However, the testing time per card for HH cards[16] (mean=0.66±0.55 min) and OCC[17] (mean=0.65±0.51 min) was found to be comparable ($p=0.07$) (table 6.15). Hiding Heidi cards were carried out as the first test in 49 children (51.04%), when compared to OCC which was carried out as the first test in 47 children (48.96%) (table 6.17).

Test	Children with CVI (n=111)			Controls (n=50)		
	Testability (%)	**Testing time (mins)**	**Testing time per card (mins)**	**Testability (%)**	**Testing time (mins)**	**Testing time per card (mins)**
Hiding Heidi cards	102 (91.8%)	0.95±0.56	0.66±0.55	50 (100%)	0.53±0.38	0.1±0.08
Ohio contrast cards	99 (89.1%)	1.23±0.66	0.65±0.51	50 (100%)	1.01±0.83	0.1±0.09

Table 6.15: Testability and testing time of contrast sensitivity tools in children with CVI (n=111) and in controls (n=50)

The engagement scores are listed below in table 6.16. Children who were not testable were not given an engagement score. A majority of the children were noted to have some meaningful to convincing results using both tests (i.e., partial and complete engagement groups). The chronological age was significantly different across the 3 levels of engagement for HH cards ($p<0.001$, Kruskall-Wallis). The age was comparable between 'no vs. partial engagement' ($p=0.2$, Mann Whitney). However, chronological age was noted to be significantly different for 'partial vs. complete' engagement groups (p:0.005, Mann Whitney) and between 'no vs. complete engagement' groups ($p=0.03$, Mann Whitney). Children in the 'complete engagement' group (mean=4.01±2.34 years) were found to be significantly older than the 'partial engagement' group (mean=2.49±1.66 years) and the 'no engagement' group (mean=1.81±1.5 years).

[16] *6 levels of contrast*
[17] *12 levels of contrast*

Results

The chronological age was significantly different across the 3 levels of engagement using OCC (p=0.04, Kruskall-Wallis). The age was comparable between 'no vs. partial engagement (p=0.89, Mann Whitney). However, chronological age was noted to be significantly different for 'partial vs. complete engagement' groups (p<0.001, Mann Whitney) and between 'no vs. complete engagement' groups (p=0.06, Man Whitney). Children in the 'complete engagement' group (mean=3.74±2.35 years) were found to be significantly older than the 'partial engagement group' (mean=2.53±1.65 years) and the 'no engagement group' (mean=1.89 2.74±1.05 2.01 years).

CVI				**Controls**			
Test	**Score 0** ***(No engagement)***	**Score 1** ***(Partial engagement)***	**Score 2** ***(Complete engagement)***	**Test**	**Score 0** ***(No engagement)***	**Score 1** ***(Partial engagement)***	**Score 2** ***(Complete engagement)***
Hiding Heidi cards (n=102)	11 (10.7%)	69 (67.6%)	22 (21.5%)	Hiding Heidi cards (n=50)	0 (0%)	0 (0%)	50 (100%)
Ohio contrast cards (n=99)	8 (8.1%)	69 (69.6%)	22 (22.2%)	Ohio contrast cards (n=50)	0 (0%)	9 (18%)	41 (82%)

Table 6.16: Engagement scores for Hiding Heidi and Ohio contrast cards in children with CVI and in controls

Parents/caregivers reported that the child would like to perform the test again if required using HH cards (84.3%) and OCC (86.8%) in 86 children. No fatigue/boredom was noted in 84 children (82.3%) using HH cards when compared to 87 children (87.8%) using OCC on feedback from the parents/caregivers. The effect of the order of testing on engagement score was not significant using HH cards (p=0.86, Chi-square) and OCC (p=0.7, Chi-square) (table 6.17). Only 2 (4.3%) and 3 children (6.1%) were noted to be in the 'no engagement' group when HH cards and OCC were tested second in the order.

Engagement score	**Hiding Heidi (first test) (n=49)**	**Hiding Heidi (second test) (n=46)**	**Ohio contrast cards (first test) (n=46)**	**Ohio contrast cards (second test) (n=49)**
Score 0 *(No engagement)*	3 (6.12%)	2 (4.3%)	5 (10.8%)	3 (6.1%)
Score 1 *(Partial engagement)*	36 (73.4%)	33 (71.7%)	31 (67.3%)	35 (71.4%)
Score 3 *(Complete engagement)*	10 (20.4%)	11 (23.9%)	10 (21.7%)	11 (22.4%)

Table 6.17: Order of testing of contrast sensitivity tests categorised based on the engagement ratios in children with CVI (n=95)

b. Controls

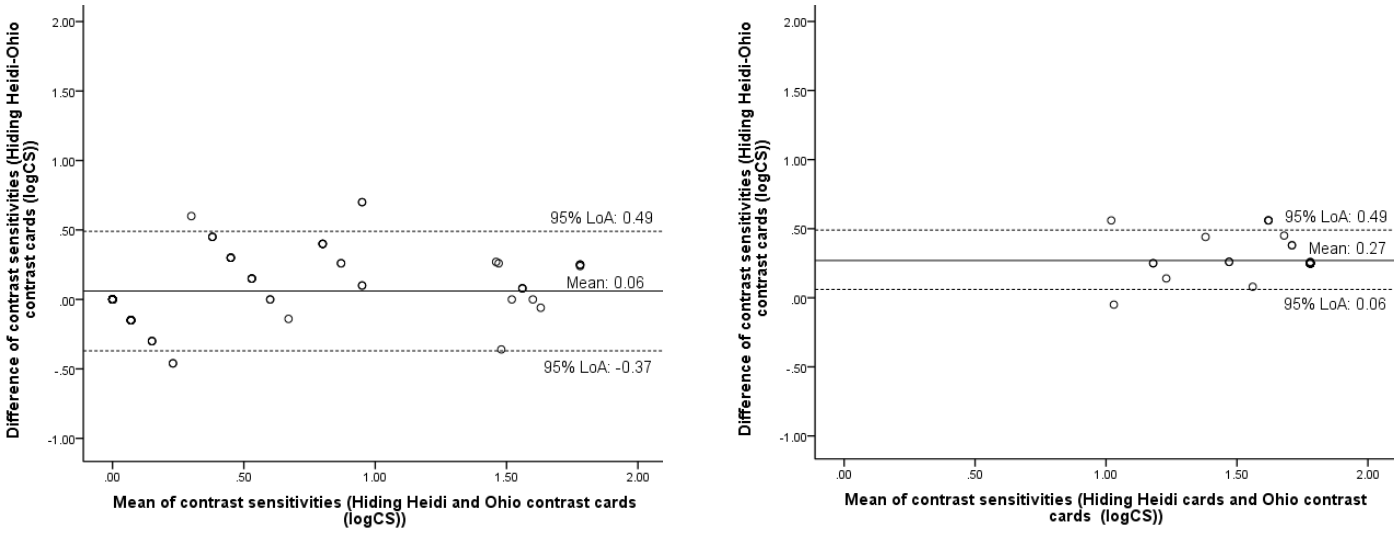
Contrast sensitivity testability rates were found to be comparable with HH cards and OCC (100%). The HH cards were found to be significantly faster to administer than OCC ($p<0.01$). The testing time per card for HH cards (mean=0.1±0.08 min) and OCC (mean=0.1±0.09 min) were comparable ($p=0.59$, Wilcoxon) (table 6.15). The testing time per card for HH cards was noted to be significantly faster (~6.6 times) for controls (mean=0.1±0.08 min) when compared to children in the CVI group (mean=0.66±0.55 min) ($p<0.001$). The testing time per card for OCC was noted to significantly faster (~6.5 times) for controls (mean=0.1±0.09 min) when compared to children in the CVI group (mean=0.65±0.51 min) ($p<0.001$).

The engagement score was found to be to convincing threshold or to the finest contrast level possible in all 50 children (100%) with HH cards and in 41 children (82%) using OCC (table 6.16). All the 9 children with partial engagement in OCC had poor concentration during the testing and they were all noted to be in the younger age group (6 m to 1.5 year). This was apparent with better contrast values that were recorded using HH cards.

6.5.2 Contrast sensitivity

a. Children with CVI

The mean contrast sensitivity recorded with HH cards was 0.48±0.62 logCS (range: 0.00 to 1.9 logCS) and with OCC was 0.42±0.54 logCS (range: 0.00 to 1.66 logCS). The mean difference (HH cards-OCC): 0.06±0.22 logCS was noted to be significantly different (p-value: < 0.01) with 95% LoA: -0.37 to 0.49 logCS) (n=88) (figure 6.7a). The quantifiable CS using both tests was possible only in 88 out of 111 children (79.2%). The comparison of the CS could not be carried out on children who were ‘not appreciating demonstration card’ on either test.



(a) (b)

Figure 6.7: Bland-Altman plots of agreement between Hiding Heidi cards and Ohio contrast cards in children with CVI (n=88) (a) and in controls (n=50) (b)

The mean contrast sensitivity values with the tests and their ranges have been summarized in table 6.18.

	CVI			**Controls**	
Test	**Mean±SD (logCS)**	**Range (logCS)**	**Test**	**Mean±SD (logCS)**	**Range (logCS)**
Hiding Heidi cards (n=97)	0.48±0.62	0.00 to 1.9	Hiding Heidi cards (n=50)	1.81±0.21	1.00 to 1.9
Ohio contrast cards (n=93)	0.42±0.54	0.00 to 1.66	Ohio contrast cards (n=50)	1.54±0.21	0.74 to 1.66

Table 6.18: Mean and range of contrast sensitivity values obtained using contrast sensitivity tests in children with CVI and in controls (logCS)

The mean difference and LoA between HH cards and OCC was determined for children only in the 'complete engagement' group separately (n=19). The mean difference between HH cards and OCC was noted to be 0.12±0.18 logCS and it was noted to be significant (p=0.009, Wilcoxon) but with a narrower 95% LoA was -0.23 to 0.47 logCS.

b. Controls

The mean contrast sensitivity recorded with HH cards was 1.81±0.21 logCS (range: 1.00 to 1.9 logCS) and with OCC was 1.54±0.21 logCS (range: -0.74 to 1.66 logCS). The mean difference between the tests (HH cards-OCC) was noted to be: 0.27±0.11 logCS (95% LoA: 0.06 to 0.49, p<0.001). (figure 6.7b). The mean CS with the tests and their ranges have been summarized in table 6.4.4.

The mean differences and 95% LoA between HH cards and OCC based on 4 different chronological age categories is summarized in table 6.19 for children with CVI and controls.

Children with CVI (n=88)			**Controls (n=50)**		
Age categories	**Mean difference±SD (logCS)**	**95% LoA (logCS)**	**Age categories**	**Mean difference±SD (logCS)**	**95% LoA (logCS)**
6 months to 1 year (n=12)	-0.01±0.23	-0.46 to 0.44	6 months to 1 year (n=4)	0.3 ±0.18	-0.05 to 0.65
> 1 year to 3 years (n=42)	0.05±0.24	-0.18 to 0.28	> 1 year to 3 years (n=23)	0.31±0.15	0.02 to 0.6
> 3 years to 5 years (n=20)	0.09±0.15	-0.2 to 0.38	> 3 years to 5 years (n=12)	0.25±0.002	0.24 to 0.25
> 5 years to 7 years (n=14)	0.12±0.26	-0.38 to 0.62	> 5 years to 7 years (n=11)	0.25±0.0	0.25

Table 6.19: Mean differences and 95% limits of agreement for Hiding Heidi and Ohio contrast cards based on chronological age categories for children with CVI (n=88) and controls (n=50)

Figure 6.8 shows the CS distribution based on the chronological age of typically developing and children with CVI obtained using OCC. As earlier studies were not available for comparison, only the current study cohort's CS (95% confidence intervals) were plotted. Only 8 (8.4%) children with CVI, were noted to be within 95% confidence intervals of the controls based on chronological age.

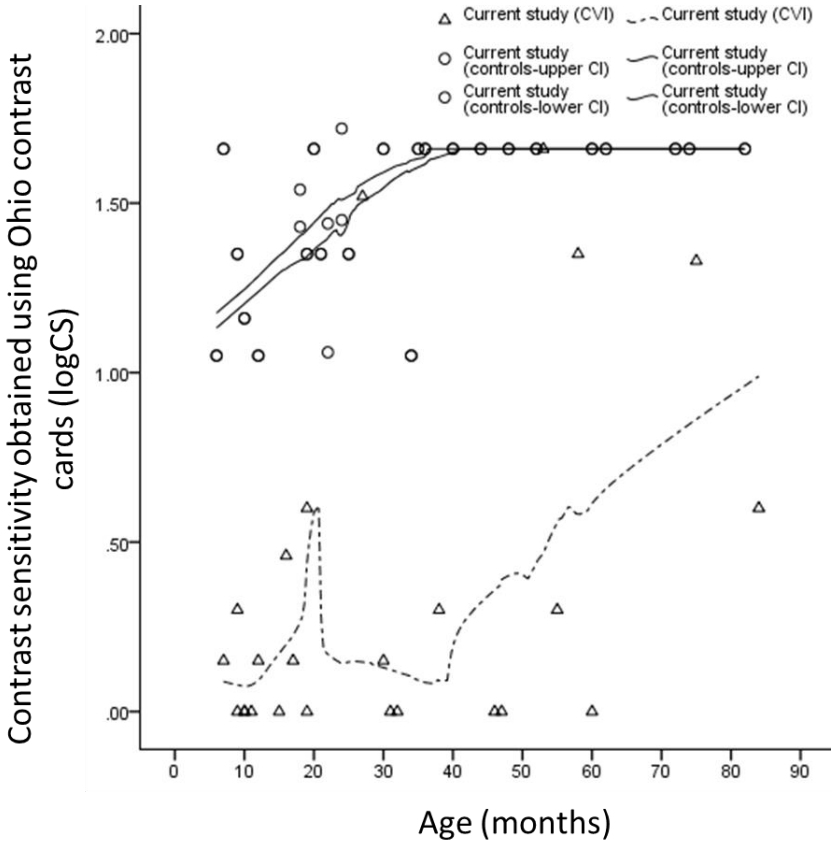


Figure 6.8: Scatter plot representing the contrast sensitivity distribution obtained using Ohio contrast cards in typically developing children (95% confidence intervals, n=50) and in children with CVI (n=95) in this study

Key findings		
Parameter	**CVI**	**Controls**
Testability	Higher with HH cards (91.8%)	Comparable between HH cards and OCC (100%)
"Complete" engagement score	Higher with OCC (22.2%)	Higher with HH cards (100%)
Testing time	Shorter with HH cards (0.95±0.56 minutes)	Shorter with HH cards (0.53±0.38 minutes)
Mean difference between HH cards and OCC	0.06±0.22 logCS	0.27±0.11 logCS
95% LoA between HH cards and OCC	-0.37 to 0.49 logCS	0.06 to 0.49 logCS
Ohio contrast cards under-estimated contrast sensitivity by 0.06 logCS in children with CVI and 0.27 logCS in controls when compared to Hiding Heidi cards		

6.5 Objective 4: Repeatability of clinical tools to measure visual functions in children with CVI and typically developing children

Intra-observer repeatability

A total of 36 children with CVI were recruited for intra-observer repeatability with a median duration of 0.5 months, mean of: 2.26±3.23 months (range: 1 day to 11 months). However, for the purpose of analysis only those children who were retested within 1 month of duration (as proposed in the protocol), were included (n=21). As there can be a confounding effect of the child's overall development based on the chronological age, children having more than 1 month retest duration were not included in this analysis.

In the control group, a total of 20 children were recruited for intra-observer repeatability with a median duration of 0.5 months, mean of: 0.8±0.81 months (range: 1 week to 3 months). However, for the purpose of analysis only those children who were retested within 1 month duration (as proposed in the protocol), were included (n=16). There was no significant difference based on the chronological age between children with CVI and control group (p=0.23, Wilcoxon).

Therefore, in total the repeatability was measured on 21 children with CVI and 16 controls. The age categories of these children were as follows: CVI: 6 months to 1 year: 2 , 1-3 years: 10 , 3-5 years: 5, 5-7 years: 4; controls: 6 months to 1 year: 2, 1-3 years: 12, 3-5 years: 2.

6.5.1 Visual acuities

a. Children with CVI

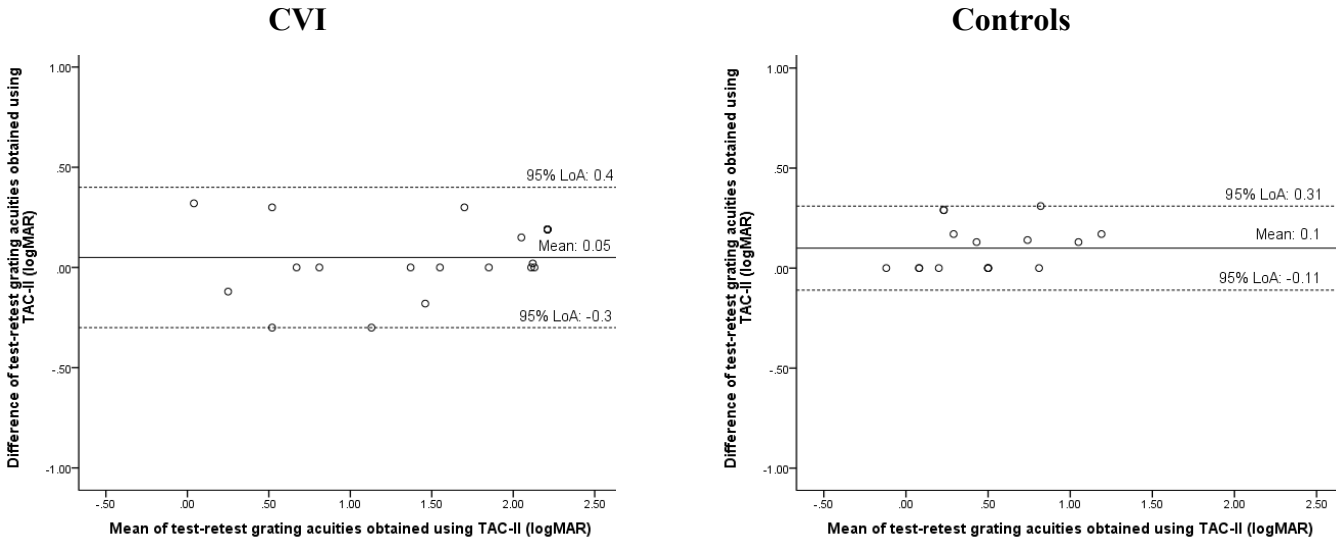
The mean age of the children was 2.98±1.87 years (range: 11 months to 6.83 years). Five children could not be tested using the PV app in the second visit. Acuities obtained using TAC-II (n=21) was noted to have narrower LoA (95% LoA: -0.3 to 0.4 logMAR, mean acuity difference: 0.05±0.18 logMAR; CR: 0.47) (figure 6.9a), when compared to the PV app (n=16) (95% LoA: -0.64 to 0.76 logMAR; mean acuity difference: 0.06±0.36 logMAR; CR: 0.99) (figure 6.9c). 76.2% and 50% of children were within 1-octave test-retest difference using TAC-II and the PV app respectively. The test-retest differences were further analysed based on the engagement scores (table 6.20). There was no significant difference noted in test-retest acuity values in the 'partial' vs. 'complete' engagement group for both TAC-II (p=0.31, Mann Whitney) and for Peekaboo Vision (p=0.15, Mann Whitney).

Engagement scores	**TAC-II** ***(mean test-retest difference in logMAR)***	**Peekaboo Vision** ***(mean test-retest difference in logMAR)***
Score 0 (no engagement)	-	-
Score 1 (partial engagement)	0.09±0.1 (n=13)	-0.05±0.43 (n=8)
Score 2 (complete engagement)	-0.01±0.25 (n=8)	0.18±0.25 (n=8)

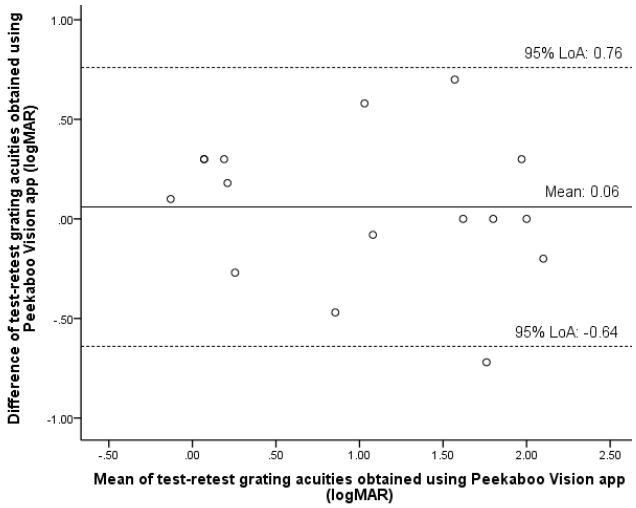
Table 6.20: Test-retest differences in acuities based on the engagement scores in children with CVI

b. Controls

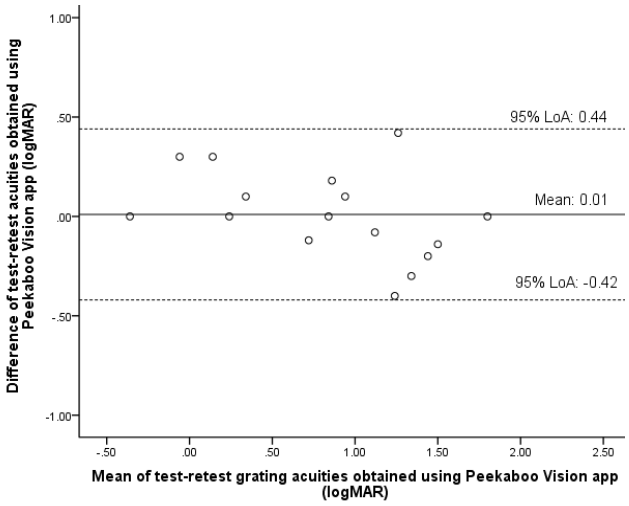
The mean age for these children was 2.54±1.52 years (range: 7 months to 6.16 years). Acuities obtained using TAC-II was noted to have better repeatability indices (95% LoA: -0.11 to 0.31 logMAR; mean acuity difference: 0.1±0.11 logMAR; CR=0.27) (figure 6.9b), when compared to PV app (95% LoA: -0.42 to 0.44 logMAR, mean acuity difference: 0.01±0.22 logMAR; CR: 0.41) (figure 6.9d). 93.7% and 68.7% of children were within 1-octave test-retest difference using TAC-II and the PV app respectively.



(a) (b)



(c)



(d)

Figure 6.9: Bland-Altman plots of agreement between test-retest acuities obtained using TAC-II in children with CVI (n=21) (a), controls (n=16) (b); using Peekaboo Vision app (c) in children with CVI (n=16) (c) and controls (n=16) (d)

6.5.2 Contrast sensitivities

a. Children with CVI

The mean age of the children was 2.98±1.87 years (range: 11 months to 6.83 years). Contrast sensitivity values using OCC (n=21) was noted to have better repeatability indices (95% LoA: -0.19 to 0.18 logCS; mean difference: -0.007±0.1 logCS; CR: 0.24) (figure 6.10a), when compared to HH cards (n=21) (95% LoA: -0.47 to 0.39 logCS; mean difference: -0.04±0.22 logCS; CR: 0.55) (figure 6.10c). The test-retest differences were further analysed based on the engagement scores (table 6.21). There was no significant difference noted in test-retest contrast sensitivity values in the 'partial' vs. 'complete' engagement group for both HH cards (p=0.76, Mann Whitney) and for OCC (p=1.00, Mann Whitney).

Engagement scores	**Hiding Heidi cards (mean test-retest difference in logCS)**	**Ohio contrast cards (mean test-retest difference in logCS)**
Score 0 (no engagement)	-	-
Score 1 (partial engagement)	-0.04±0.16 (n=14)	-0.01±0.12 (n=15)
Score 2 (complete engagement)	-0.05±0.33 (n=7)	0.0±0.0 (n=6)

Table 6.21: Test-retest differences in contrast sensitivities based on the engagement scores in children with CVI

b. Controls

The mean age for these children was 2.54±1.52 years (range: 7 months to 6.16 years). Contrast sensitivity values obtained using OCC was noted to have better repeatability indices (95% LoA: -0.07 to 0.11 logCS; mean difference: 0.02±0.05 logCS; CR=0.08) (figure 6.10b) when compared to HH cards (95% LoA: -0.26 to 0.32 logCS; mean difference: 0.03±0.15 logCS; CR: 0.27) (figure 6.10d).

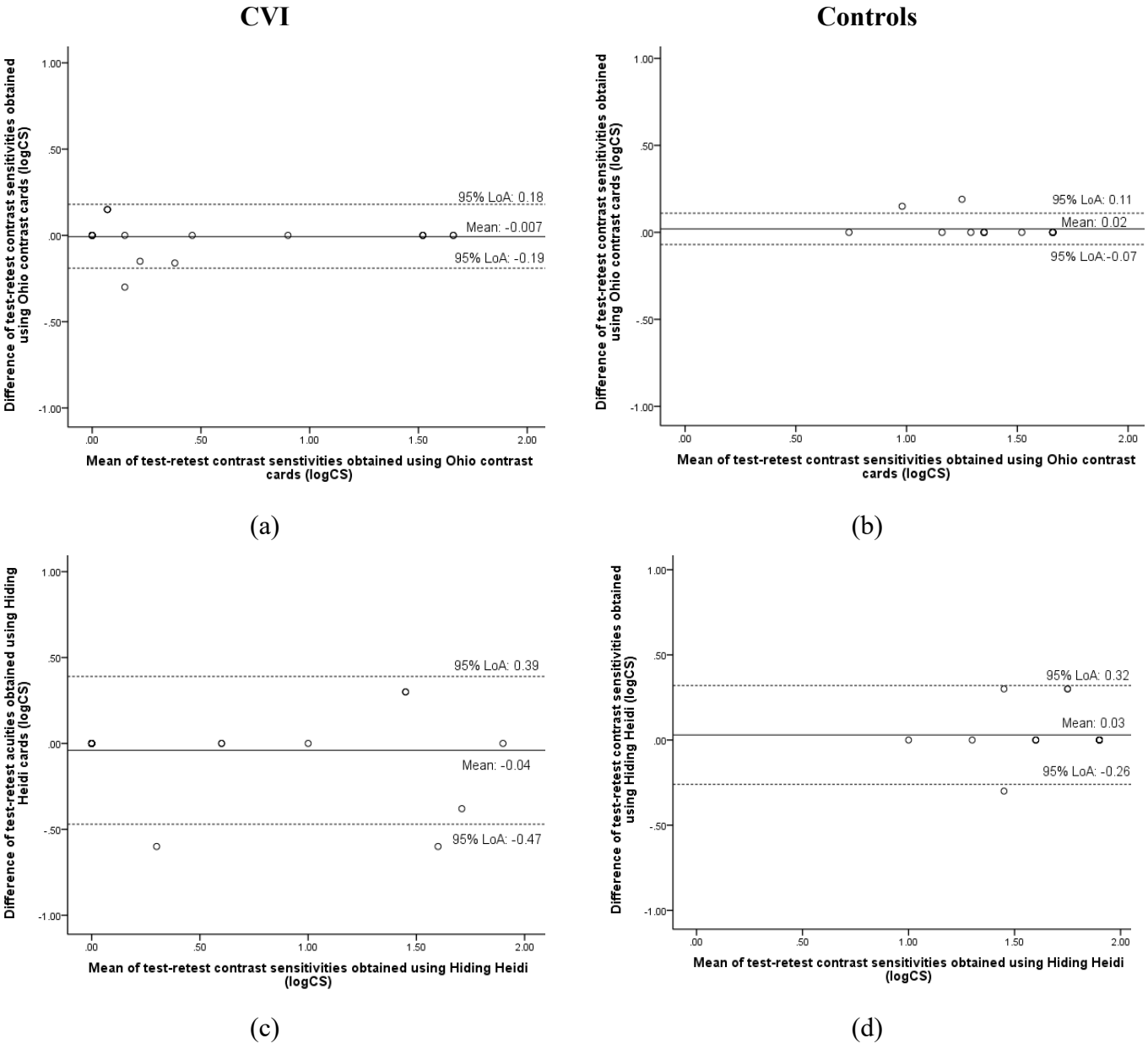


Figure 6.10: Bland-Altman plots of agreement between test-retest acuities obtained using Ohio contrast cards in children with CVI (n=21) (a), controls (n=16) (b); using Hiding Heidi cards (c) in children with CVI (n=21) (c) and controls (n=16) (d)

Key findings	
Children with CVI	**Controls**
• TAC-II *(mean test-retest difference: 0.05±0.18 logMAR, CR: 0.47 logMAR)* had better repeatability than the PV app *(mean test-retest difference: 0.06±0.36 logMAR; CR: 0.99 logMAR)*	• TAC-II *(mean test-retest difference: 0.1±0.11 logMAR, CR: 0.27 logMAR)* had better repeatability than the PV app *(mean test-retest difference 0.01±0.22 logMAR; CR:0.41logMAR)*
• OCC *(mean test-retest difference: -0.007±0.1 logCS, CR: 0.24 logCS)* had better repeatability than the HH cards *(mean test-retest difference: -0.04±0.22 logCS; CR: 0.55 logCS)*	• OCC *(mean test-retest difference: 0.02±0.05 logCS; CR=0.08 logCS)* had better repeatability than the HH *cards (mean test-retest difference: 0.03±0.15 logCS; CR: 0.27 logCS)*

6.6 Objective 5: Relationship of visual functions and associative factors

6.6.1 Functional vision

Functional vision using the CVI range instrument was assessed in a total of 108 children (84.68%). A majority of the study cohort were in the low to moderate functioning group (n=79, 73.1%). Forty-four children (40.7%) were graded as phase 1 (0-3.0 score) indicating low functioning CVI, 35 (32.4%) as phase 2 (3.25 to 7.0) indicating moderate functioning CVI and 29 (26.9%) children as phase 3 (7.25 to 10.0) indicating high functioning CVI. Chronological ages were significantly different across the 3 phases ($p<0.01$, Kruskal Wallis) of CVI, with more younger children (<3 years old) found in Phase I (80.9%).

Functional vision and association with visual concerns[18]

The association of visual concerns such as difficulty in maintaining eye contact, recognizing faces etc and functional association was studied in 94 children. One child was constantly crying and the functional vision assessment could not be carried out. The frequency distribution of all the visual concerns (including 'no visual concerns, n=6) was found to be significantly different across all 3 phases of CVI ($p=0.01$, Pearson chi-square). The distribution of the concerns across the phases is shown below in figure 6.6.1. The frequency distribution of visual concerns in individual phases: phase I and II ($p=0.5$, Pearson chi-square), phase II and III ($p=0.07$, Pearson chi-square) were found to be comparable. Phases I and III were found to be significantly different ($p=0.01$, Pearson chi-square). Among the 28 children whose parents reported more than one visual concern, the distribution of the concerns by phases was as follows: phase I, n=12 (42.9%); phase II, n=11 (39.3%); phase III, n=5 (17.9%).

The top two visual concerns: difficulty in recognizing faces (phase I, n= 16 (41%); phase II, n=12 (38.7%)) had almost similar percentages in phase I and II and maintaining eye contact was found to be the most common concern in phase 2 (n=14, 45.2%). The third highest visual concern of unable to look or track lights primarily was found in phase I (n=9, 23.1%). Children in phase III (i.e., those who had better function) primarily had concerns with missing objects in the lower/side field (n=6, 25%) and eye deviation (n=6, 25%) (figure 6.11).

[18] *This paper "Parent-reported visual concerns in children with cerebral visual impairment presenting to a paediatric neurology clinic" is published in the Journal of Clinical Optometry in July 2023 (A15)*

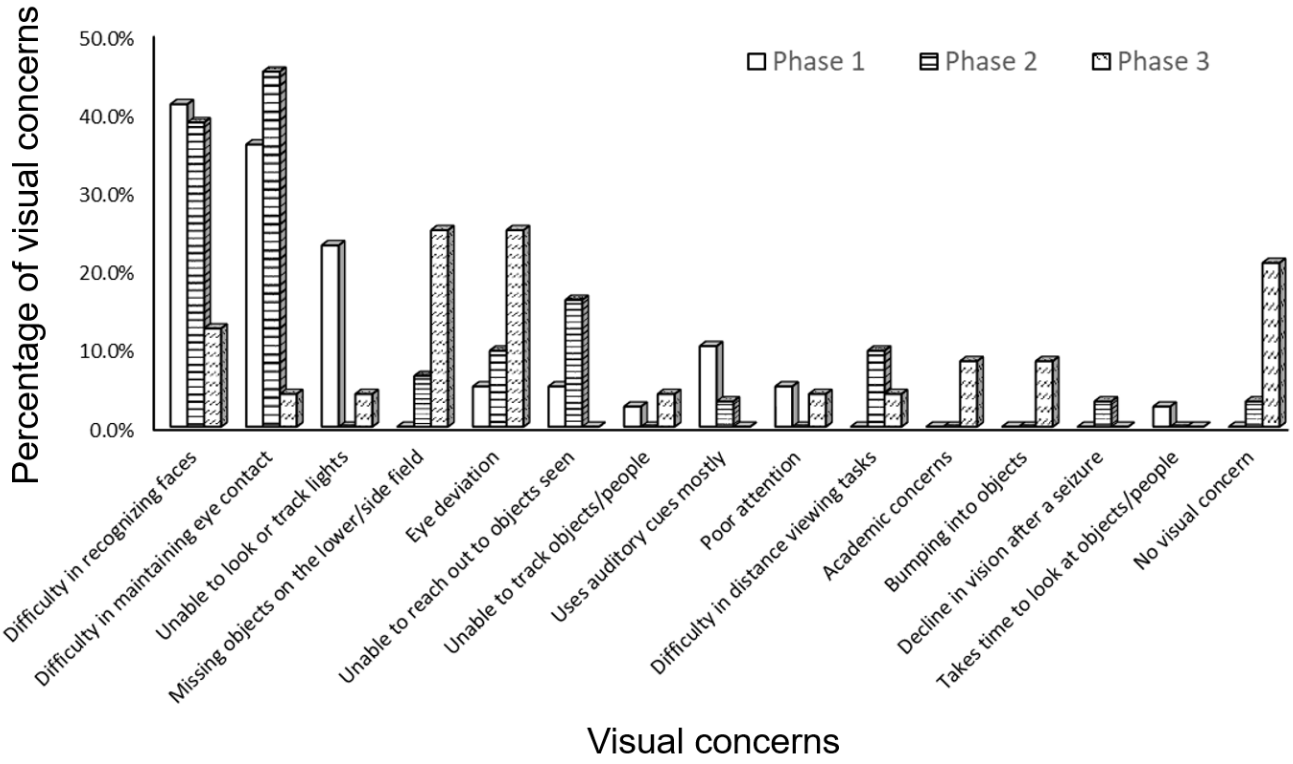
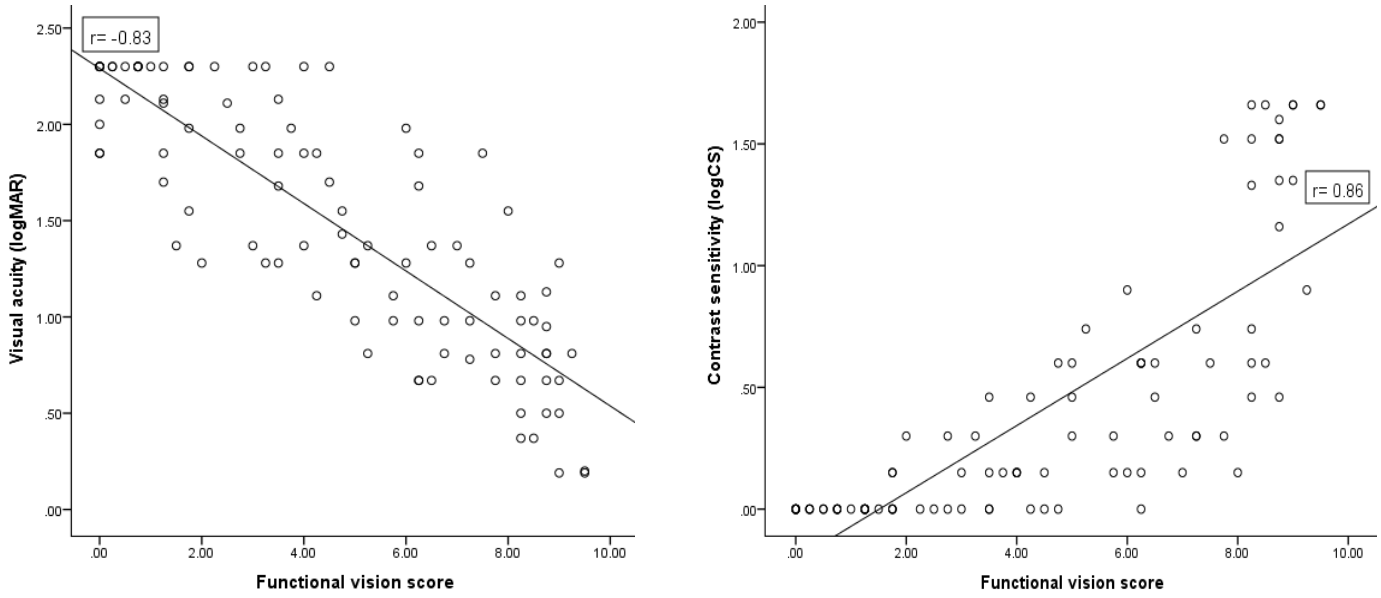


Figure 6.11: Clustered bar graph representing the frequency distribution of visual concerns reported by parents based on the functional vision (n=94)

(Note: Visual concerns are more in number than the sample, as some parents (n=28) reported more than one visual concern)

Functional vision and association with visual functions

Visual acuity and CS measurements obtained on the first visit using TAC-II and OCC respectively were used for this analysis, as these tests were found to have better repeatability indices. The functional vision score was strongly and significantly correlated with VA (TAC-II: r= -0.83, r^2=0.68, p<0.001, Spearman's rho, n=98) and with CS (OCC: r=0.86, r^2=0.73, p<0.001, Spearman's rho, n=93)) (figure 6.12).



(a) (b)

Figure 6.12: Scatter plot demonstrating correlation between functional vision score and visual acuity (a) and contrast sensitivity (b)

Both VA and CS were found to be significantly different across the 3 phases of CVI ($p<0.01$), when adjusted for age using linear mixed model analysis (table 6.22), with the children with poorer acuity and CS in phase I. In those children with CVI, whose parents did not report any visual concern (n=6, 5.5%), the range of VA was from 0.19 to 1.28 logMAR and CS was 1.3 to 0.6 logCS. Five of them were in phase III and one in phase II based on their functional vision assessment.

For further analysis with functional vision and chronological/developmental age, TAC-II and OCC cards have been used unless stated otherwise. The VA, CS and chronological age were used in a multiple regression analysis to predict the functional vision score. The prediction model was statistically significant ($F(3, 84) = 82.7$, $p <0.001$) and accounted for approximately 73.8% of the variance of functional vision score. The regression analysis for each predictor variable when other 2 predictors are controlled for is as follows: For every 1.0 logMAR increase (i.e., worsening) in VA, there was a significant decrease in the functional vision score by 3.15 points ($\beta= -3.15$, $p<0.001$). For every 1.0 logCS increase (i.e., better) in CS value, there was an increase in the functional vision score by 1.14 points ($\beta=1.14$, $p=0.05$), however, not significantly. However, for every one-month increase in age, only a small but not significant increase in the functional vision score by 0.008 points was noted ($\beta= 0.008$, $p=0.39$).

Grading of CVI	Number of children (%) (n=108)	Chronological age	Visual acuity (mean logMAR): TAC-II	Contrast sensitivity (mean logCS): OCC
Phase I (0-3) Building visual behaviour	44 (40.7%)	2.15±1.38 (8 m to 7 years)	2.06±0.3 (1.28 to 2.3) Does not appreciate demo=8 & not testable =2	0.03±0.08 (0.00 to 0.3) Does not appreciate demo=5 & not testable =5
Phase II (3.25-7.0) Integrating vision with function	35 (32.4%)	2.73±1.71 (7 m to 6.3 years)	1.44 ±0.48 (0.67 to 2.3)	0.3±0.25 (0.00 to 0.9) Does not appreciate demo=1 Not testable=2
Phase III (7.25 to 10.0) Resolution of CVI characteristics	29 (26.9%)	4.35±1.81 (9 m to 7 years)	0.8±0.4 (0.19 to 1.85)	1.07±0.54 (0.15 to 1.66) Not testable=3

Table 6.22: Distribution of children based on the CVI phases along with chronological age and visual functions (n=108)

The multiple regression analysis was carried out by using developmental age as one of the predictors along with VA and CS for predicting functional vision score (n=52). The distribution of the developmental age across the 3 phases of CVI is summarized in table 6.23. The prediction model was statistically significant ($F(3, 48) = 62.6$, $p < 0.001$) and accounted for approximately 78.4% of the variance of functional vision score. The regression analysis for each predictor variable when other 2 predictors are controlled for is as follows: For every 1.0 logMAR increase (i.e., worsening) in VA, there was a significant decrease in the functional vision score by 3.78 points ($\beta = -3.78$, $p<0.001$). However, for every 1.0 logCS increase (i.e., better) in CS value, there was an increase in the functional vision score by only 0.15 points and it was not significant ($\beta = 0.15$, $p=0.85$). For every one-month increase in developmental age, only a small and insignificant increase in the functional vision score by 0.017 points was noted ($\beta = 0.017$, $p=0.4$).

The mean difference of VA between PV app and TAC-II was studied based on the CVI phases (n=78, phase I=17, phase II=34 and phase III=27). The mean difference in phase I was -0.14±0.48 logMAR, phase II was -0.26±0.42 logMAR and phase III was -0.3±0.31 logMAR. There was no significant difference across the 3 phases ($p=0.23$, Kruskal-Wallis) and between phase I vs. II ($p=0.45$, Mann-Whitney) and phase II vs. III ($p=0.32$, Mann-Whitney). However, the difference was tending towards significance between phase I vs. III ($p=0.07$, Mann-Whitney), indicating that the difference between

the tests is wider in phase I when compared to phase III. The mean difference of CS between HH cards and OCC was studied based on the CVI phases (n=88, phase I=33, phase II=31 and phase III=24). The mean difference in phase I was 0.02±0.13 logCS, phase II was 0.05±0.27 logCS and phase III was 0.14±0.25 logCS. The difference was tending towards significance across the 3 phases (p=0.06, Kruskal-Wallis) and was significant between phase I vs. III (p=0.005, Mann Whitney), indicating that the difference between the tests were smaller for phase I and II and wider for phase III. There was no significant difference between phase I vs. II (p=0.76, Mann-Whitney) and phase II vs. III (p=0.27, Mann-Whitney).

6.6.2 Developmental quotient/age [19]

The developmental quotient/age data was available in 57/111 children. The description of DDST-2 that was used to grade the developmental quotient has been discussed in section 5.6.2. The developmental quotient and developmental age ranged from 8.0 to 101.0[20] and from 2.86 months to 6.9 years respectively. The mean developmental age was 1.46±1.37 years. The distribution of the developmental age based on CVI phases is given in table 6.23.

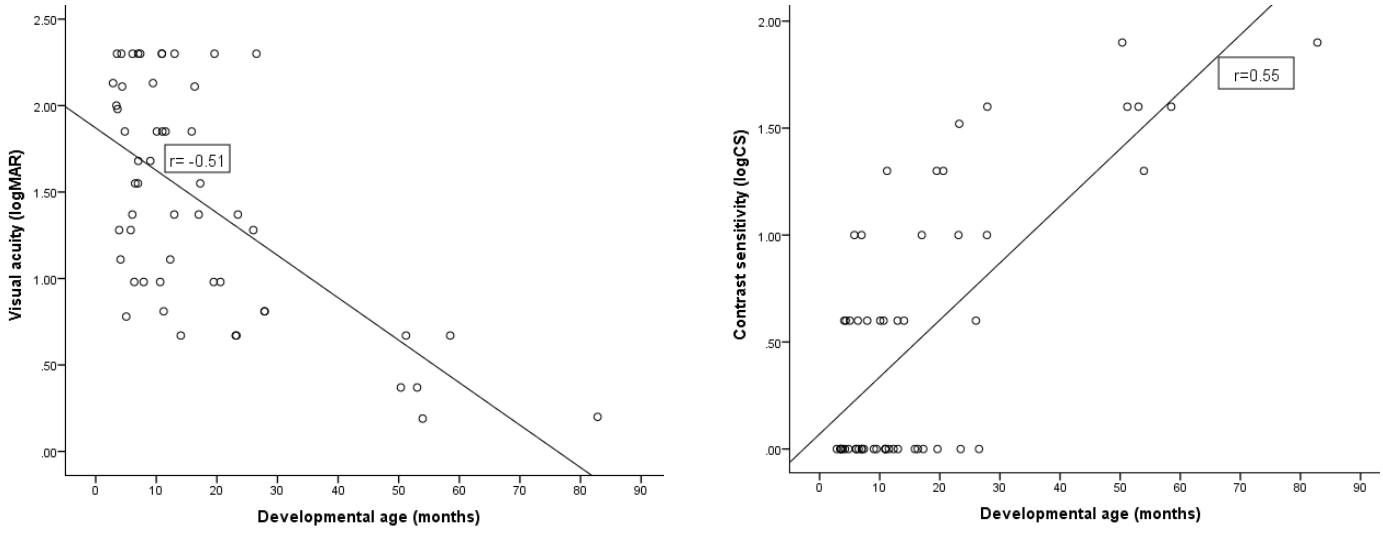
Grading of CVI	**Number of children (%) (n=57)**	**Chronological age**	**Developmental age**	**Visual acuity (mean logMAR): TAC-II**	**Contrast sensitivity (mean logCS): OCC**
Phase I (0-3) Building visual behaviour	19 (33.33%)	2.15±1.38 (8 m to 7 years)	0.71±0.48 (2.86 m to 2.21 years)	2.13±0.21 (1.55 to 2.3) Does not appreciate demo=1	0.01±0.04 (0.00 to 0.15) Does not appreciate demo=1 Not testable=1
Phase II (3.25-7.0) Integrating vision with function	21 (36.84%)	2.73±1.71 (7 m to 6.3 years)	0.96±0.48 (3.87 m to 1.95 years)	1.33 ±0.42 (0.67 to 2.3)	0.32±0.25 (0.00 to 0.74) Does not appreciate demo=1 Not testable=1
Phase III (7.25 to 10.0) Resolution of CVI characteristics	17 (29.82%)	4.35±1.81 (9 m to 7 years)	2.91±1.37 years (5.04 m to 6.9 years)	0.79±0.37 (0.19 to 1.85)	1.03±0.57 (0.15 to 1.66) Not testable=1

Table 6.23: Distribution of children with CVI across 3 phases of CVI along with visual functions and chronological and developmental ages (n=57)

[19] *Scientific poster was presented in the Association for Research in Vision and Ophthalmology (ARVO), May 2022 (A8)*

[20] *Arbitrary units*

Using linear mixed model analysis (chronological age adjusted), the outcome parameters of VA, CS and developmental age were compared to the CVI phases. Significant differences were noted across the 3 phases of CVI for VA and CS ($p<0.01$). There was no significant difference between phase 1 and 2 based on developmental age ($p=0.47$), however, developmental age of phase 3 was significantly different when compared to the other 2 phases ($p<0.01$). The visual functions (VA and CS) were found to be moderately and significantly correlated with developmental age (VA: $r= -0.54$, $r^2=0.43$, $p<0.001$, $n=56$ and CS, $r= 0.59$, $r^2=0.66$, $p<0.001$, $n=52$) (figure 6.13). The functional vision score was noted to have strong and significant correlation with developmental age ($r=0.71$, $r^2=0.41$, $p<0.001$, $n=57$) (figure 6.14). Whereas chronological age had moderate and significant correlation with VA ($r= -0.42$, $r^2=0.22$, $p<0.001$, $n=95$), CS ($r=0.46$, $r^2=0.33$, $p<0.001$, $n=90$) and the functional vision score ($r=0.49$, $r^2=0.24$, $p<0.001$, $n=108$).



(a) (b)

Figure 6.13: Scatter plots demonstrating correlation between developmental age and visual acuity (a) and contrast sensitivity (b) (n=53)

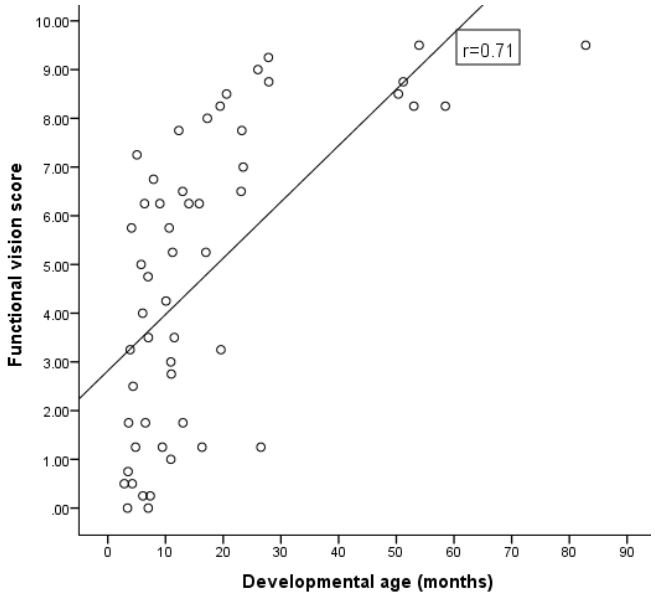
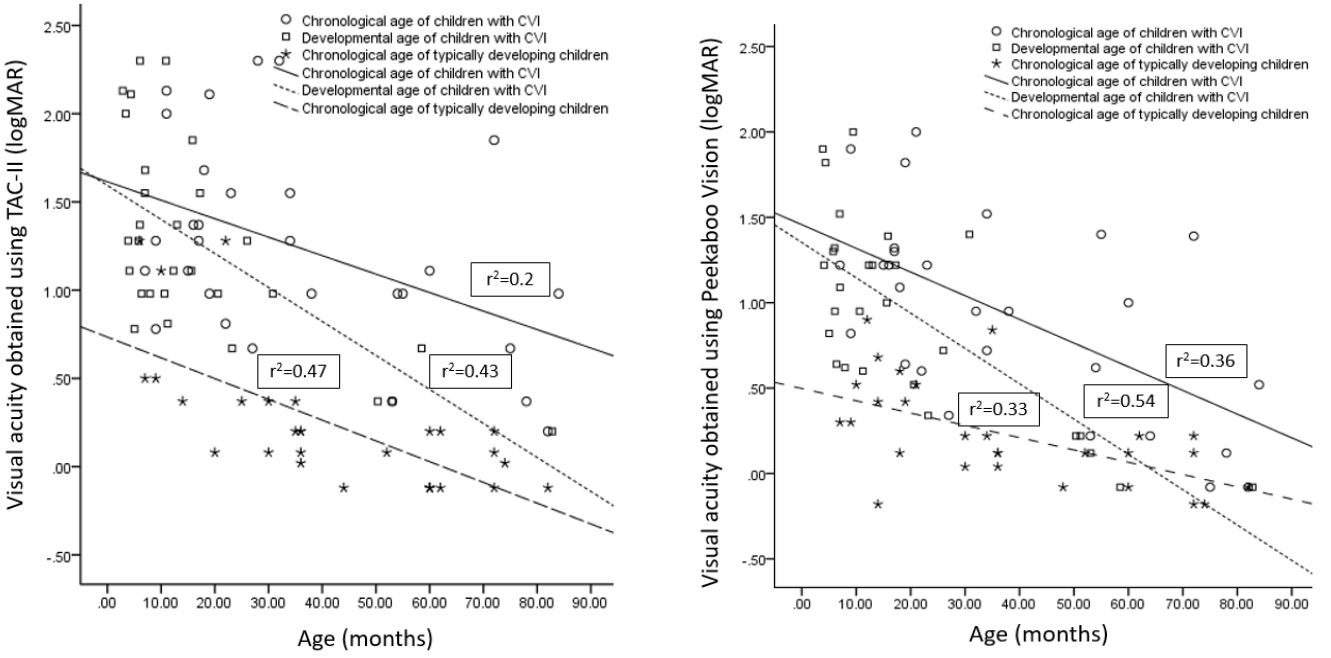


Figure 6.14: Scatter plot demonstrating correlation between functional vision score and developmental age (n=53)

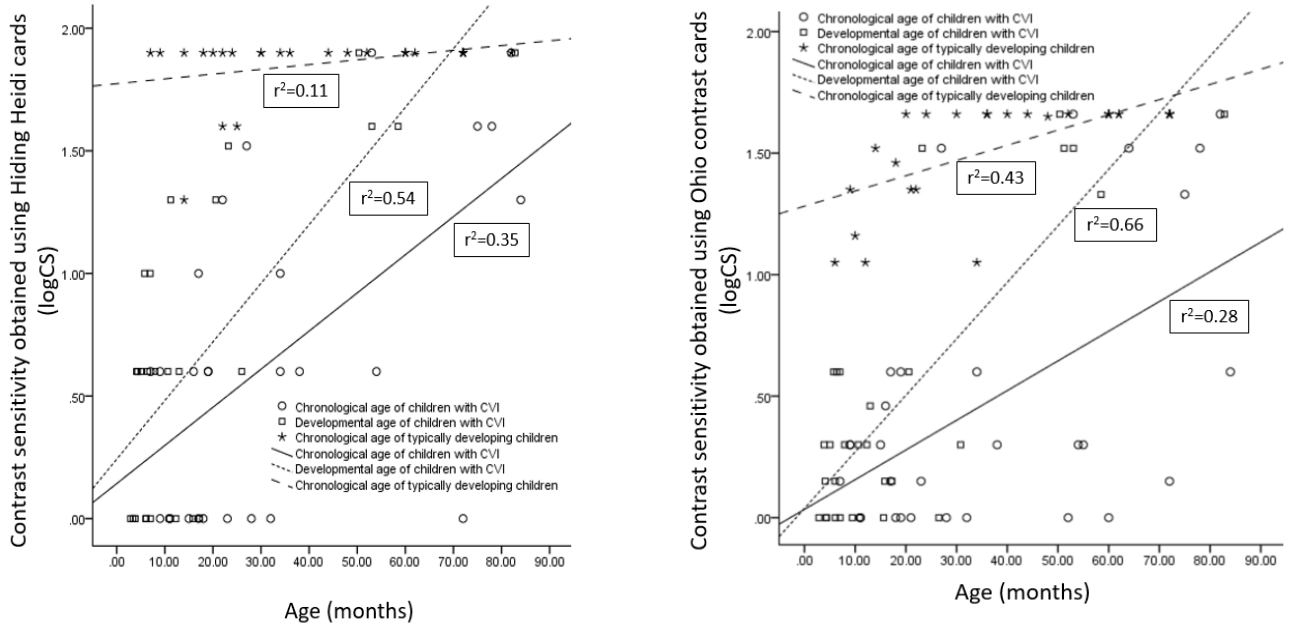
Further analysis was carried out to determine the effect of chronological and developmental age on visual functions (VA and CS) in children with CVI. This was compared against age-similar controls (n=50). Using TAC-II (56/111) and PV (44/111), the VA regardless of the test used was better predicted by the developmental age (TAC-II, r^2=0.43; PV, r^2=0.54) than chronological age (TAC-II, r^2=0.2; PV, r^2=0.36). Whereas in controls, the chronological age (TAC-II, r^2=0.47; PV, r^2=0.33) could explain the variability similarly to that of the developmental age of children with CVI. (figure 6.15a and b).

Using HH cards (53/111) and OCC (52/111), the CS was better predicted by the developmental age (HH cards, r^2=0.54; OCC, r^2=0.66) than chronological age (HH cards, r^2=0.35; OCC, r^2=0.28). Whereas in controls, the increase in chronological age could explain only 11% of improvement with chronological age using HH cards (r^2=0.11) and 43% with OCC (r^2=0.43) (figure 6.16a and b).



(a) (b)

Figure 6.15: Scatter plots representing the distribution of visual acuity based on the chronological and developmental ages of children with CVI and controls using TAC-II (a) and Peekaboo Vision app (b)



(a) (b)

Figure 6.16: Scatter plots representing the distribution of contrast sensitivity based on the chronological and developmental ages of children with CVI and controls using Hiding Heidi cards (a) and Ohio contrast cards (b)

The effect of chronological and developmental age on functional vision score was studied. This data was studied in 52/111 children with CVI. An increase in developmental age was found to explain the functional vision score better (r^2=0.41, p<0.001, Spearman's rho) than the chronological age (r^2=0.26, p<0.001, Spearman's rho) (figure 6.17).

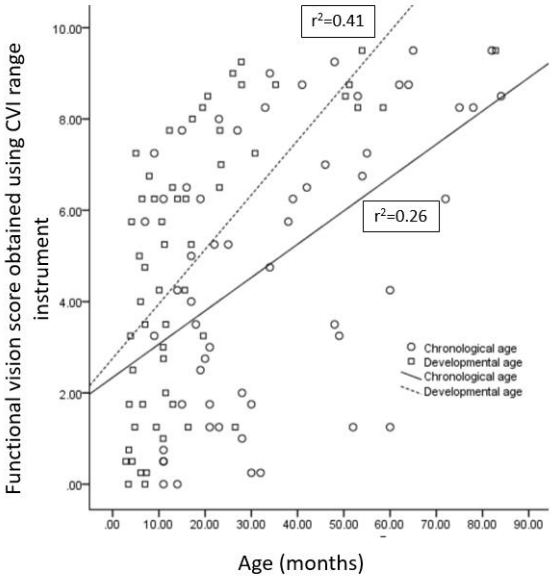
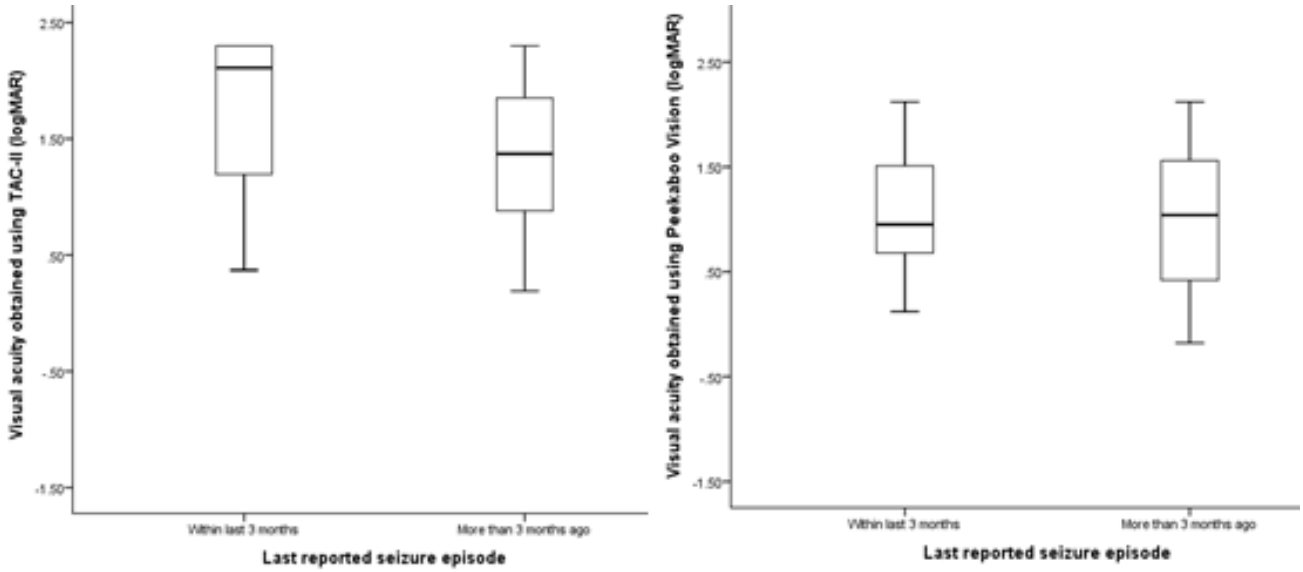


Figure 6.17: Scatter plot representing the distribution of functional vision score obtained using CVI range instrument based on the chronological and developmental ages of children with CVI

6.6.3 Seizure frequency

The seizure frequency vs. visual functions data was available for different tests as follows: TAC-II= 63/111, PV app=47/111, HH cards=62/111 and OCC=59/111. The last seizure episode as reported by the parents was noted (see table 6.3) and the children were categorized into 2 groups: (i) last seizure episode reported within and including 3 months duration (group 1) and last seizure episode reported more than 3 months ago (group 2). This criteria was chosen based on the findings by Wong et al, who noted poor prognosis in children who had uncontrolled seizures for 3 months following the initial brain insult (Wong, 1991). The chronological (n=71, p=0.19, Mann-Whitney) and developmental ages (n=37, p=0.63, Mann-Whitney) were noted to be comparable between both groups.

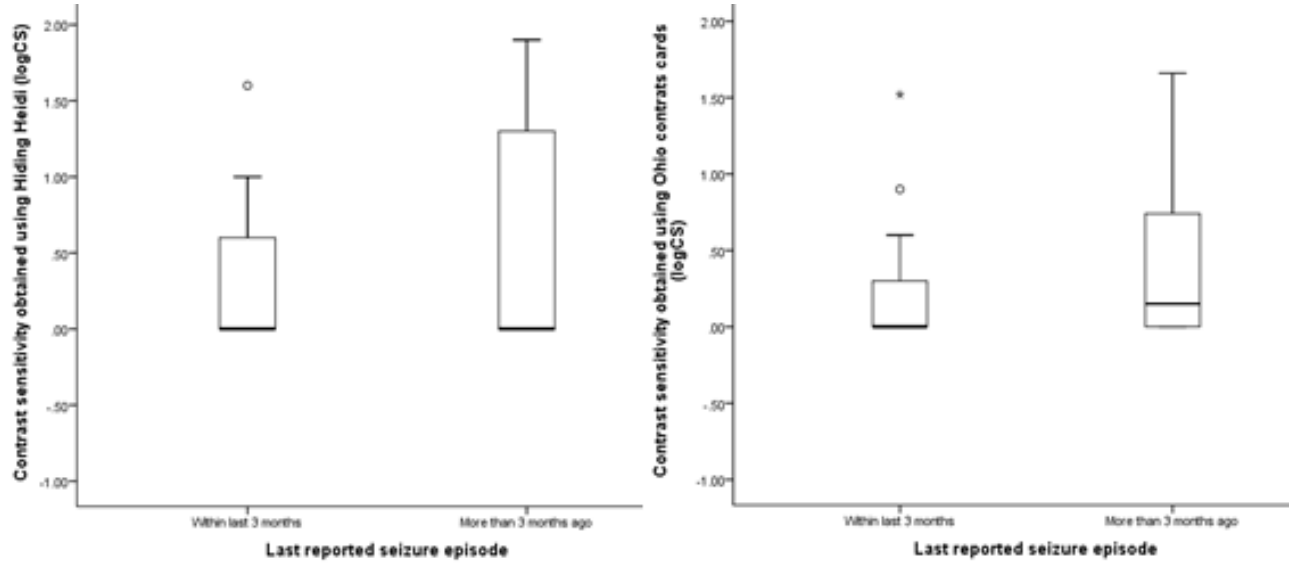
The VA recorded using TAC-II was noted to be significantly better in those children who had last seizure episode more than 3 months ago (n=63, p=0.03, Mann-Whitney) (group 1, n=26 and group 2, n=37) (figure 6.18a). Both groups were comparable using PV app (n=47, p=0.84, Mann-Whitney) (group 1, n=17 and group 2, n=30) (figure 6.18b).



(a) (b)

Figure 6.18: Boxplots representing the visual acuity obtained using TAC-II (n=63) (a) and Peekaboo Vision (n=47) (b) based on the last reported seizure episode

The CS was noted to be comparable using HH cards (n=62, p=0.1, Mann-Whitney) (group 1, n=26 and group 2, n=36) (figure 6.19 a) and significantly better using OCC in those children with last seizure episode more than 3 months ago (n=59, p=0.02, Mann-Whitney) (group 1, n=24 and group 2, n=35) (figure 6.19b).



(a) (b)

Figure 6.19: Boxplots representing the contrast sensitivity obtained using Hiding Heidi (n=62) (a) and Ohio contrast cards (n=59) (b) based on the last reported seizure episode

The functional vision score was noted to be significantly better in those children who had last seizure episode more than 3 months ago (n=71, p=0.008, Mann-Whitney) (group 1, n=31 and group 2, n=40) (figure 6.20).

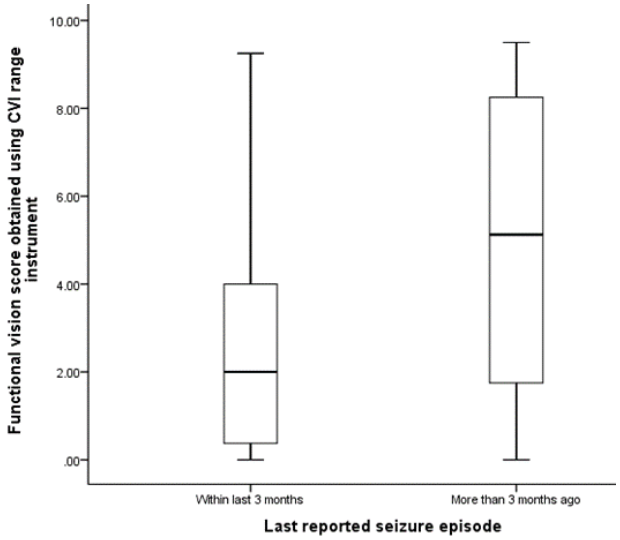


Figure 6.20: Boxplot representing the functional vision score obtained using CVI range instrument (n=71) based on the last reported seizure episode

6.6.4 Refractive error

The association of refractive error with VA (using TAC-II, n=35), CS (using HH cards, n=35) and functional vision (n=34) was studied in children with CVI. Age-appropriate refractive correction were noted in (n=14, 40%) of the children. For analysis purposes, the eye with least amount of spherical equivalent was chosen. The correlation of refractive error with the visual functions and functional vision was weak (spherical equivalent vs. VA (r=-0.13, r^2 = 0.02, p=0.57, Spearman's rho) vs. CS (r=0.06, p=0.74, r^2 = 0.004, Spearman's rho), vs. functional vision score (r=0.026, p=0.88, r^2 = 0.0001, Spearman's rho).

6.6.5 Brain imaging

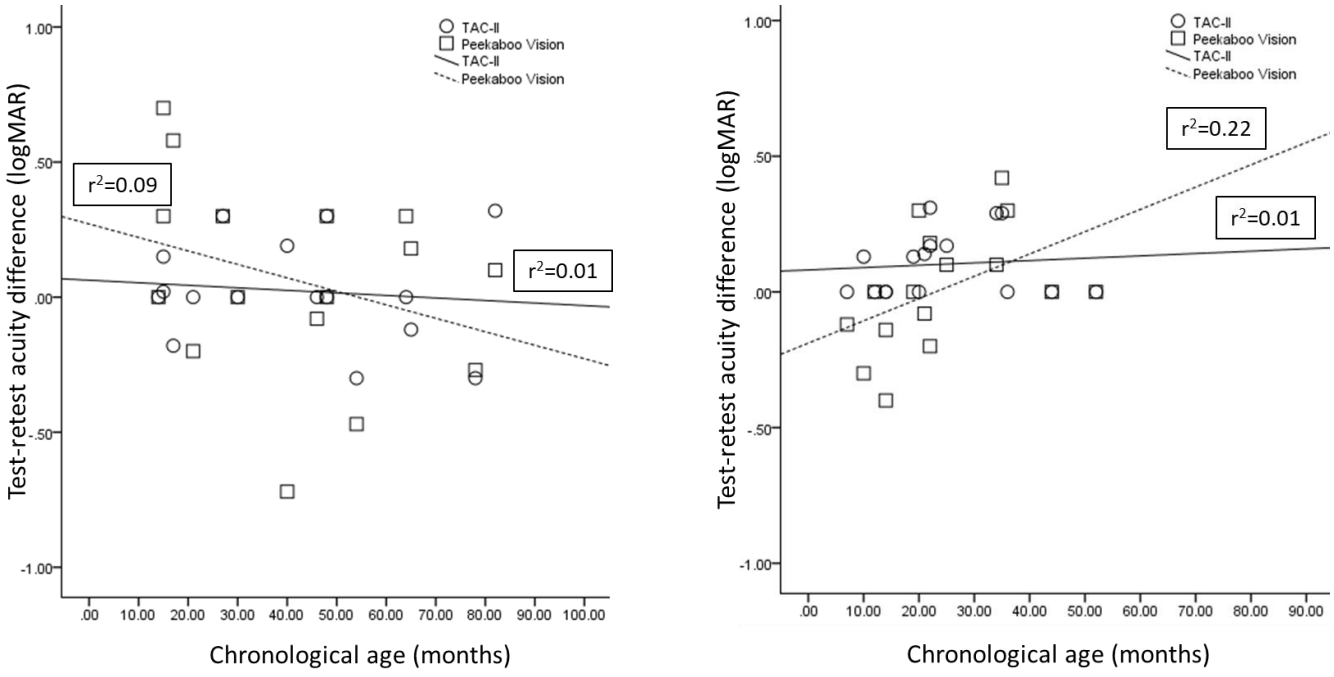
The association between the brain imaging score and visual functions (using TAC-II and HH cards) and functional vision score was studied in 30 children. A weak correlation was found between the overall brain imaging score vs. VA (r=-0.04, r^2=0.01), vs. CS (r=0.004, r^2=0.002) and vs. functional vision score (r=0.03, r^2=0.01). On only using the optic radiations score for analysis, weak correlation was noted with the visual functions: VA (r=-0.27, r^2=0.1, p=0.17), vs. CS (r=0.16, r^2=0.04, p=0.4). However, 16/24 (66.6%) children with moderate to severe optic radiations damage, had acuity <1.0 logMAR. For functional vision score, although a weak correlation but tending towards significance

was obtained (r=0.36, r^2=0.13, p=0.06). On using occipital lobe/visual cortex scoring, similar results of weak correlation between the vision-related parameters were observed: VA (r=-0.32, r^2=0.14, p=0.09), vs. CS (r=0.11, r^2=0.06, p=0.56) vs. functional vision (r=0.17, r^2=0.05, p=0.39). However, 13/20 (65%) children with moderate to severe occipital lobe/visual cortex damage, had acuity <1.0 logMAR.

6.6.6 Repeatability of visual functions and associative factors

Chronological age

The association of repeatability of visual functions were studied with relation to chronological age. This data was available in 21/21 using TAC-II and in 16/17 using PV app in children with CVI and 16/16 children for both tests in the control group. The difference was not found to be significantly different with TAC-II (p=0.15, Chi-square) and with PV app (p=0.16, Chi-square) based on the chronological age in children with CVI (figure 6.21a). The difference was not found to be significantly different in the controls as well with TAC-II (p=0.37, Chi-square) and with PV app (p=0.53, Chi-square) based on the chronological age (figure 6.21b).



(a) (b)

Figure 6.21: Scatter plots representing the association between the test-retest acuity difference (using TAC-II and Peekaboo Vision app) based on the chronological age in children with CVI (a) and controls (b)

The association of test-retest CS values with chronological ages were available in 21/21 children on both groups of children. The difference was not found to significant with HH cards (p=0.14, Chi-square) nor with OCC (p=0.55, Chi-square) (figure 6.22a). The difference was not found to be significantly different in the controls with HH cards (p=0.19, Chi-square) and with OCC (p=0.19, Chi-square) based on the chronological age (figure 6.22b).

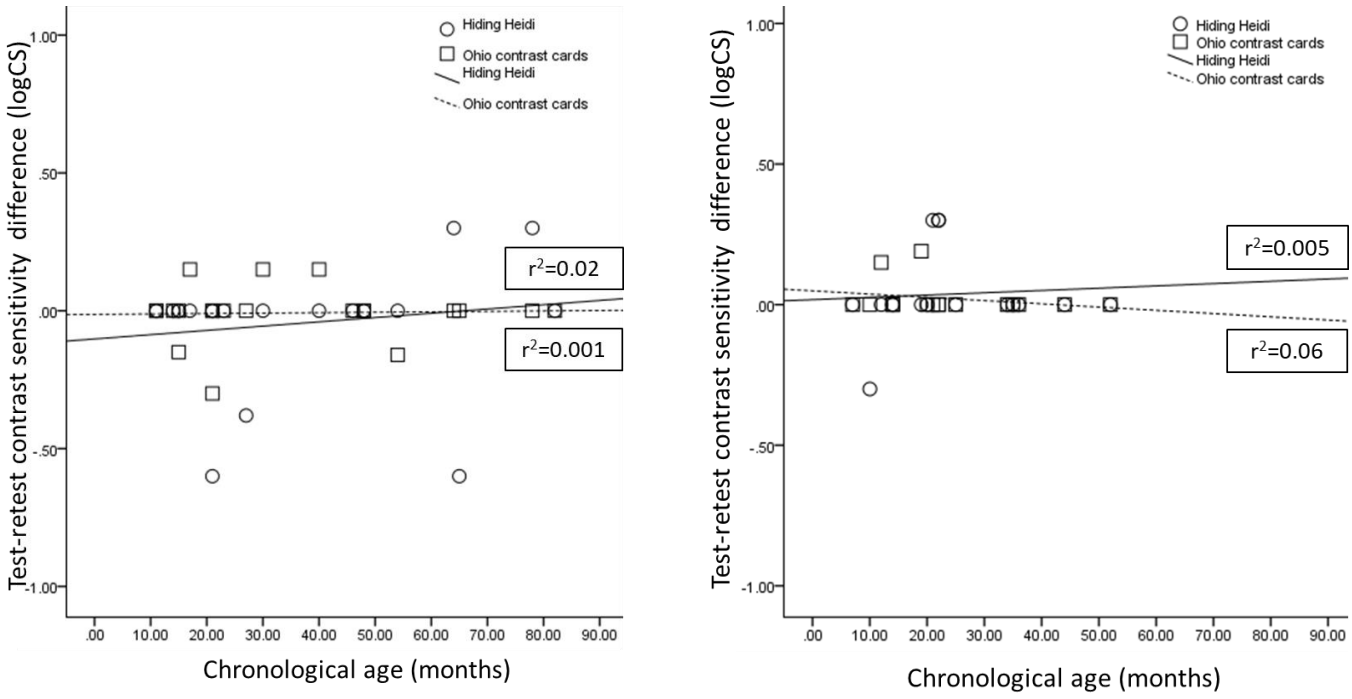
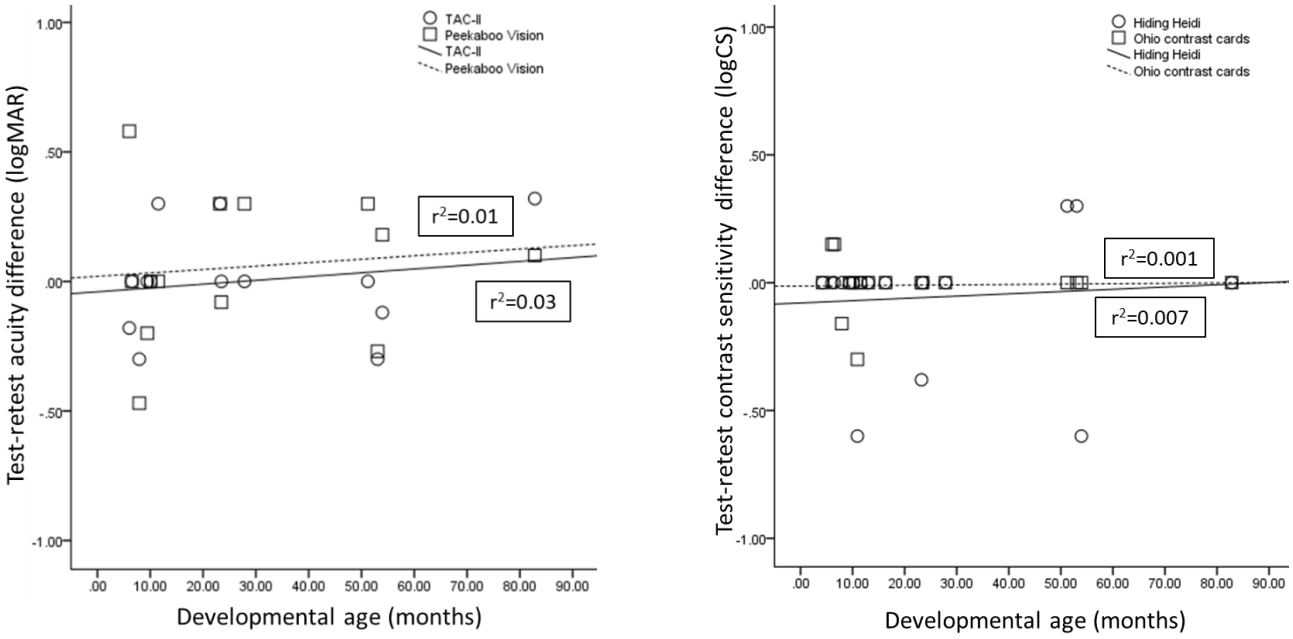


Figure 6.22: Scatter plots representing the association between the test-retest contrast sensitivity difference (using Hiding Heidi and Ohio contrast cards) based on the chronological age in children with CVI (a) and the controls (b)

Developmental age

The association of repeatability of visual functions were studied with relation to developmental age. This data was available in 17/21 using TAC-II, HH cards and OCC and 13/21 using PV app. The difference was not found to be significantly different with TAC-II (p=0.31, Chi-square), PV app (p=0.27, Chi-square), HH cards ((p=0.35, Chi-square) and OCC (p=0.35, Chi-square) based on the developmental age of children with CVI (figure 6.23a and b)

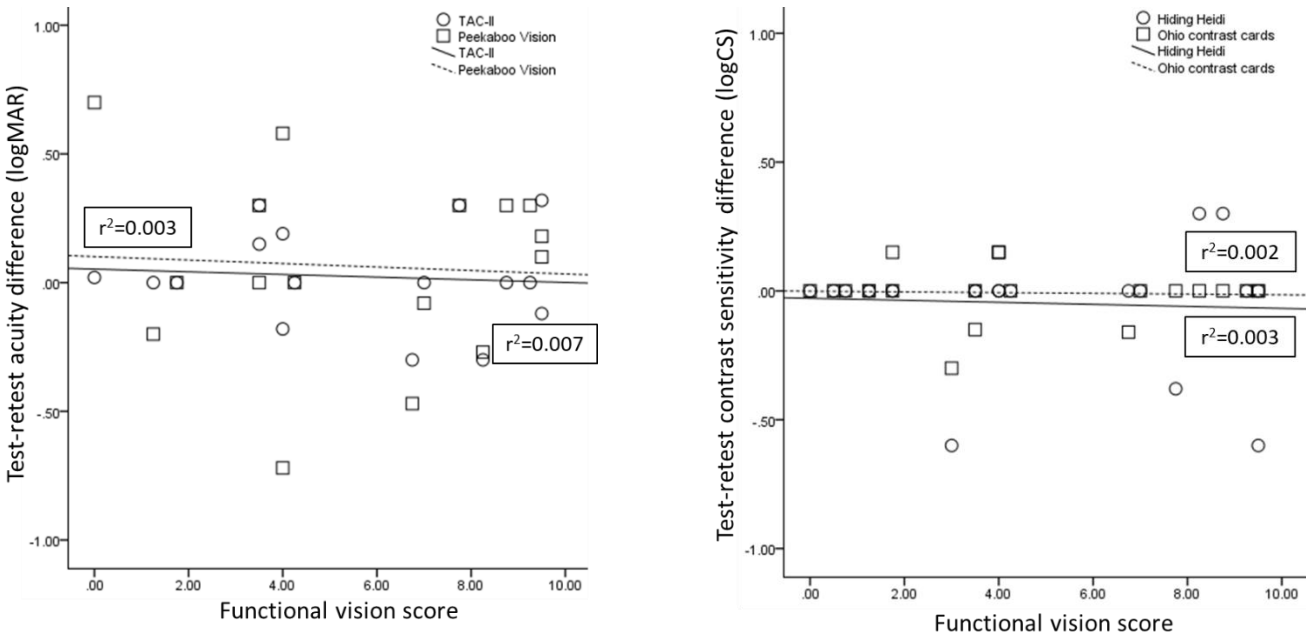


(a) (b)

Figure 6.23: Scatter plots representing the association between the test-retest difference of visual acuity (a) and contrast sensitivity (b) based on the developmental age in children with CVI

Functional vision

The association of repeatability of visual functions were studied with relation to functional vision score. This data was available in 21/21 using TAC-II, HH cards and OCC and 16/21 using PV app. The data for the test-retest of VA using TAC-II (p=0.61, Chi-square) and PV app (p=0.39, Chi-square) was not found to be significantly different based on the functional vision score (figure 6.24a). The data for the test-retest of contrast sensitivities using HH cards (p=0.1, Chi-square) and OCC (p=0.2, Chi-square) was not found to be significantly different based on the functional vision score (figure 6.24b).



(a) (b)

Figure 6.24: Scatter plots representing the association between the test-retest difference of visual acuity (a) and contrast sensitivity (b) based on the functional vision score in children with CVI

Seizure history

The association of repeatability of visual functions were studied with relation to the last reported seizure episode, i.e., last seizure episode reported within and including 3 months duration (group 1) and last seizure episode reported more than 3 months ago (group 2). This data was available in 17/21 using TAC-II, HH cards, OCC (group 1=6, group 2=11) and 13/21 using PV app (group 1=4, group 2=9). There was no significant difference in the test-retest acuity differences (TAC-II, p=0.1; PV, p= 0.75 Mann Whitney) and for CS (HH cards, p=0.31; OCC, p=0.12, Mann Whitney).

Key findings

- Visual acuity, contrast sensitivity and developmental age are the best predictors for functional vision score
- Visual acuity and contrast sensitivity are moderately and significantly correlated with developmental age
- Functional vision score is strongly and significantly correlated with developmental age
- Developmental age explains the change in visual acuity and in contrast sensitivity better than chronological age
- Visual acuity and contrast sensitivity measures are more variable in children with frequent episodes of seizures

Chapter 7 : Discussion

7.1 Chapter overview

In the chapter 6, the results for each of the five study objectives were reported. In the current chapter, these findings will be discussed in detail and compared against any existing literature, to aid accurate data interpretation, facilitate the advancement of knowledge and to translate for clinical practice. Section 7.2 will discuss how the current study cohort's demographics and clinical characteristics compare with other studies relating to children diagnosed with CVI. Sections 7.3 and 7.4 will include a discussion about the validation of VA and CS tools in children with CVI and in other cohorts of SEN and/or VA and CS tests on typically developing infants and young children. Section 7.5 will focus on comparing the repeatability indices of VA and CS tools in children with CVI against other groups of children. The final section 7.6 will discuss findings of the relationship between VA and CS and other parameters such as functional vision, developmental age, seizure history, neuroimaging and refractive error and how they compare against the findings of earlier reported studies.

7.2 Demographics and clinical characteristics

7.2.1 Demographic characteristics

In this study, children with CVI were recruited primarily from the paediatric neurology clinics (n=84) and a smaller minority from the paediatric vision rehabilitation centre of a tertiary eye institute (n=27). The age of presentation was found to be significantly younger for those children who presented to the neurology clinic (2.81±1.88 years) in comparison to the eye institute (3.46±1.63) (p=0.03, Mann Whitney). The primary aim of this presentation could be attributed to neurological signs such as seizures and/or delayed developmental milestones in several domains, which are easy for parents to identify and this could have resulted in them consulting a paediatrician who would then refer to the paediatric neurology clinics. In several other studies from ophthalmology clinics, the mean age of presentation was noted to be variable: 5.24±4.61 years (Pehere et al., 2018), 5.5±3.55 years (Galli et al., 2022), 3.8 years (median: 3 years) (Philip et al., 2016) and 1.4 years (median: 0.9 years) (Kelly et al., 2021). However, presentation was noted at a younger age in neurology clinics (mean age: 1.56±1.4 years) (Jimenez-Gomez et al., 2022). These findings are consistent with our current study. This implies that there is a need to improve early referrals to the ophthalmology and vision rehabilitation centres for comprehensive evaluation and to initiate necessary management, such as: refractive correction, squint surgery and vision rehabilitative measures, in order to make the best use of the active neuroplasticity in the critical period of life (Idil et al., 2021). The higher prevalence of squint (85.4%), optic atrophy (72.2%) and correctable refractive errors (40%) in the current study also suggest the importance of comprehensive eye evaluation. A retrospective review of medical records of children with CVI was

carried out to understand the risk factors for poor recovery of vision and revealed that older age of presentation was noted to be the primary factor contributing to poor recovery (median age of presentation: 1.13 years, range: 2.9 months to 6.36 years) (Handa et al., 2018).

In the current study, there was a higher prevalence of males (70.2%). A similar higher trend was observed in other studies that included CVI (62% (Pehere et al., 2019), 64.5% (Pehere et al., 2018), 58.9% (Fazzi et al., 2007)) and other SEN groups (62.16% (Sumalini et al., 2022), 62.1% (Woodhouse et al., 2003)) from different geographical locations. In children with learning disability, the skewed gender distribution was noted as well and attributed to the physiological difference in the male and female brains suggesting that the latter use more cortical areas as part of their learning processes (Galaburda, 2011; Haddad, 2017). In children with autism spectrum disorder, the inability of gene compensation in boys when compared to girls was noted (Nguyen et al., 2020). However, no specific reason for the higher prevalence of males in the CVI group was listed. An equal gender distribution in the control group would have been ideal. One third of children (38%) were recruited from local children's home and this home has reportedly higher proportion of girls than boys in general. This resulted in unequal gender distribution in the control group (girls: 62% and boys: 38%). However, there were no significant differences in the chronological age (p=0.44, Mann Whitney) and visual function (VA, p= 0.06; CS, p=0.82, Mann Whitney) measures between both groups.

7.2.2 Clinical characteristics

Aetiologies

Neonatal hypoglycaemic brain injury (47.61%) was noted to be the most common aetiology in this cohort, followed by HIE (24.76%), genetic (8.57%) and PVL (7.61%). Several previous studies have found that HIE is the most common aetiology of CVI (Huo et al., 1999; Malkowicz et al., 2006; Pehere et al., 2018) followed by PVL in premature babies (Fan et al., 2006; Good et al., 2001). However, in the current study, we found that NHBI was the primary cause of CVI and the reasons for these differences in aetiologies are unclear. Regular monitoring of blood glucose levels is part of the postnatal care of screening at-risk babies in the developed countries (Harding et al., 2017). However, this continues to be a challenge in developing countries due to the significant scope of improvement needed in the perinatal care delivery (Udani et al., 2009). Gestational diabetes can also be a risk factor for developing NHBI (Güemes & Hussain, 2015). In the current study, only 2 mothers (6.6%) reported having this condition. This low percentage could raise possibilities of gestational diabetes being undiagnosed or under-diagnosed. Hypoxic ischemic encephalopathy can occur either due to hypoglycemic or non-hypoglycemic reasons (Parmentier et al., 2022) and therefore, the clinician should elicit suitable

questions about child's birth history to differentiate the cause for HIE and to confirm the aetiology of NHBI. In the current study, specific questions about hypoglycemic history in the neonatal period were elicited. This could have led to NHBI being better highlighted when compared to Pehere et al's retrospective review of medical records in which HIE was noted to be the most common cause of CVI (Pehere et al., 2018).

Birth, family and medical history

In the current study, only 2 children were noted to be extremely preterm (i.e., <28 weeks) and 9 in the very preterm range (i.e., 28 to 32 weeks), whereas 40 children were born preterm (i.e., <37-33 weeks). Our study is in agreement with another study carried out in a different South Indian state wherein 40 children (32.3%) were noted to be preterm (<34 weeks) (Pehere et al., 2018). A majority of the children in the current study were delivered through caesarean section (72.8%). There could be several perinatal reasons for planning a caesarean section such as fetal distress, intrauterine growth retardation, meconium aspiration etc (Ganesh et al., 2019). However, these have not been captured in this study. While the relationship between mode of delivery and CVI has not been studied to the best of our knowledge, the mode of delivery was found to play a role in hypoglycaemic episodes in neonates (Dias & Gada, 2014). In a study carried out on 100 mothers and neonates in rural India in order to understand the various factors influencing the blood glucose levels in neonates, it was observed that mode of delivery could also play a role in the blood glucose levels of newly born babies. The mean blood glucose levels of babies delivered via caesarean section was lower when compared to those who were delivered vaginally (Dias & Gada, 2014). Vaginal delivery can cause more metabolic stress to the neonate when compared to caesarean section and this is likely to release catecholamines which in turn increase the blood glucose levels (Dias & Gada, 2014). Delay in breastfeeding in deliveries via caesarean sections could be due to shifting the mother from the operation theatre thereby resulting in lower glucose levels, compared to babies delivered vaginally as they are breastfed within half an hour of birth (Hawdon et al., 1992; Kayiran & Gurakan, 2010). Consanguinity was reported in 14/78 (17.9%) of the children with CVI. This can be attributed to the lesser percentage of children with genetic causes of CVI (8.5%) recruited in the current study, when compared to other causes such as NHBI and HIE. Consanguinity in the current study was also lower than a higher proportion (45.3%) of history of consanguinity in parents among children with paediatric neurological conditions, such as seizure disorders, developmental delays in multiple areas (Maheshwari & Wadhwa, 2016).

In the current study, approximately 38.7% of children were noted to have additional neurological abnormalities (see table 6.2). Neurological abnormalities that include embryological deviations

(encephalocele), cortical developmental malformations (lissencephaly - *also called smooth brain due to severely reduced gyral and sulcal malformations* (Syed, 2015) and schizencephaly – *congenital clefts extending over the cerebral hemispheres from the pial surface to the lateral ventricles and lined by cortical gray matter* (Denis et al., 2000)), peri/intra ventricular hemorrhages, neonatal encephalopathy and cerebral ischemia have been noted. These congenital malformations could lead to damage to the visual pathways (Hoyt & Taylor, 2012), resulting in vision impairment and higher-order visual deficits due to dorsal and/or ventral stream dysfunctions (Bennett et al., 2020).

Electroencephalography and seizures

Seizures are common in children with CVI and most children use one or more antiepileptic medications (Huo et al., 1999). A large majority of children in our study (80%) had a history of seizures and most (96%) were on antiepileptic medication. Seizures have also been noted to be the cause of CVI, primarily due to infantile spasms (Good et al., 1994). In some cases, CVI could also result as a transient ictal[21] or postictal consequence (Kosnik et al., 1976). The seizure type can vary in this group of children, from recurrent seizures to occasional or none. Seizure activity can interfere with visual functions (Huo et al., 1999), particularly in the hypsarrhythmic stage, a sharp decline in vision has been observed in children with CVI (Miller & Walsh, 1982). Prompt treatment of seizures and altering the dosage of the medication can have a positive effect on visual functions, emphasizing the need for close monitoring (Good et al., 1994; Huo et al., 1999). The current study has not looked into the relationship between the seizure type and visual functions, as it was beyond the scope of this study. The relationship between the frequency of seizure episode and vision-related parameters have been determined and discussed (see section 6.6.3). As EEG was performed only at the first visit and therefore studying the change in the visual functions with the change in the seizure activity was not possible. However, it would be interesting to study this in future work.

Developmental concerns and rehabilitation therapies

In the current study, a large proportion of parents reported their children to have delay in several developmental milestones, i.e., vision, motor, speech and cognition (n=81, 72.9%). A very similar developmental profile was noted in children with CVI in another study conducted in the South India (Pehere et al., 2019). While auditory issues can also be present in children with CVI (11%) (Khetpal & Donahue, 2007), in the current study only 1 child was reported to have hearing loss. However, no formal assessment was carried out as part of the study and it may well be possible that other children

[21] *Ictal is the time period from the first symptom of seizure to the end of seizure activity*

had auditory impairment. In contrast with our findings, a retrospective study carried out on children diagnosed with CVI reported a relatively higher percentage of children had hearing impairment (24/196, 12%) i.e., hearing threshold above 25dB (Bosch et al., 2014).

Literature suggests that a large proportion (60-70%) of children with cerebral palsy have CVI (Schenk-Rootlieb et al., 1994). In the current study, there was no specific assessments carried out to diagnose cerebral palsy. However, the diagnosis of static encephalopathy (also referred as cerebral palsy) was diagnosed in 19/43 (44.1%) in the current study. However, no specific MRI grading was carried out to diagnose cerebral palsy (such as: Magnetic Resonance Classification System by Surveillance of Cerebral Palsy in Europe (Himmelmann et al., 2020)) A higher proportion of children with motor delays in our study (68.4%) is a good indicator to suspect cerebral palsy. However, there were no traditional developmental checklists used in this study that are commonly administered by rehabilitation professionals for children with cerebral palsy, for example: Gross Motor Function Classification System (GMFCS) for gross motor skills, Manual Ability Classification System (MACS) for fine motor skills (Early assessments and screenings for cerebral palsy), Bayley Scales of Infant Development (BSID) for overall development (Lee et al., 2013) and Viking speech scale for speech assessment (Pennington et al., 2013). Therefore, it is difficult to ascertain if any of the children from the study cohort had cerebral palsy although this could have been the case. Children with cerebral palsy due to high prevalence of upper limb impairment are likely to have restriction in giving a motor response such as clicking on the screen during testing with the PV app.

Despite the high proportion of children with developmental delays in the current study (84.6%), only a very small proportion of parents reported availing therapies for their children (n=9, 8.1%) and out of which only 4 (44.4%) sought professional help. Five parents reported carrying out home-based therapies by themselves. Travel concerns and financial constraints were stated as reasons for not availing office-based rehabilitative therapies by the parents. Lack of availability of trained professional locally was also one of the important reasons for not initiating/continuing therapies. Few of these concerns have also been reported in a study conducted on parents of children with developmental delay in Rajasthan, India. the most common reasons stated by the parents for not seeking support included: belief system (such as accepting the child's condition as his/her destiny and being uncertain of the benefits of rehabilitation), time concerns, family issues (such as other household responsibilities and job transfer) and socioeconomic concerns (Mishra & Siddharth, 2018). These reasons, highlight the importance of increasing the numbers of trained rehabilitation professionals in order to improve coverage of services, enabling better levels of education for parents and caregivers about the long-term

consequences of the child's condition and the potential benefits of the rehabilitative therapies. Another reason stated in the current study is that parents prioritize seizure control, which is essential for the child's overall development (Jimenez-Gomez et al., 2022).

In a recent scoping review by Delay et al (Delay et al., 2023), a total of 6 distinct intervention strategies have been discussed. The strategies included were transcranial electrical stimulation, task/environmental adaptations, acupuncture and visual skills training. These are in addition to stem cell transplantation and visual stimulation therapy. Most studies included were case-reports and there were only 3 randomized controlled trials. The authors concluded that there was a need for high-quality studies with larger sample sizes to establish the effectiveness of the evidence-based interventions in this challenging cohort (Delay et al., 2023). In designing such RCTs and other high-quality studies, the appropriate clinical tools should be identified that are repeatable and validated. This study has identified tools for two important visual functions. Teller acuity cards-II for VA and OCC for CS assessment.

Visual concerns

In the current study, fourteen unique visual concerns have been identified children with CVI with the most common ones being difficulty in maintaining eye contact and recognizing faces. This finding is consistent with the earlier literature where face identification was reported as one of the concerns in children with CVI (Bauer et al., 2023). In older children, in addition to concerns with eye contact, parents also reported about the child missing objects in the lower/side field. This could lead to bumping into objects as in ocular vision impairment conditions (Bibby et al., 2007). Several other CVI specific concerns have been reported in the literature including difficulty in identifying one toy from several of them, difficulty in looking at a person's face and paying attention to the conversation at the same time and inability to see all the information on the television screen. Only parents of 2 children reported academic related concerns in the current study, as majority of the study cohort was less than 3 years old (n=55, 57.8%) and were not of school-going age (figure 6.2).

Open style single question was used as part of this study to ask about visual concerns. This approach helps in eliciting immediate visual concerns that the parents have about the child, whereas a questionnaire could bring out aspects of the child's visual functioning that may not have been easily noticed by the parents and could be more comprehensive. Open style single question was considered appropriate in the current study given the time constraints due to the lengthy battery of tests employed as part of the primary objective of the study. Visual concerns were attempted to be elicited prior to

visual assessment procedures. However, in a small number of children (n=17), the assessment procedures were carried out first as the children were restless due to poor attention span and time constraints mentioned by parents to report back to the neurology clinic or for any other tests advised. Therefore, in those children, the visual concerns could not be elicited and this has been acknowledged as a limitation.

Children of parents who did not report any vision concern (n=6, age range: 2.83 to 5.41 years) had an acuity range between 0.19 (close to normal) to 1.28 logMAR (severe vision impairment) and CS ranging from 0.6 (profound contrast loss) to 1.66 (normal/near normal) logCS. Poorer acuity and CS values were noted in the younger age groups (i.e., 1.28 logMAR at 2.83 years and 0.6 logCS at 3.5 years). This indicates that parents/caregivers may not always be able to identify visual concerns in children with CVI even if their acuity and contrast are reduced. Developmental delays in other milestones such as motor and speech, could make it harder for parents/caregivers to notice visual problems. Therefore, a comprehensive history covering the visual concerns is essential to plan rehabilitative strategies better (Philip & Dutton, 2014). The clinician suggesting immediate guidance/strategies at the time of diagnosis was considered to be a vital component of good clinical care for children with CVI (Pilling, 2023). An easy to remember 3-word strategies based on the common visual concerns of children with CVI is summarized by Piling et al. Few examples include: 'Big Bold Bright' as a contrast enhancing strategy, 'Just One Thing' as a strategy to deal with visual crowding and 'Slow The Pace' as one of the strategies for visual latency (Pilling, 2023). Other rehabilitative strategies should also be considered wherever needed, for e.g., for children who often miss things present in their lower field, it may be helpful to change the positioning of the objects higher and for those who have difficulty in reaching out to objects seen, therapies to improve eye-hand coordination and visual spatial awareness skills maybe helpful.

Refractive correction and eye health assessment

Literature suggests that CVI can occur in isolation or could be associated with ocular disorders (Jacobson & Dutton, 2000; Pehere & Jacob, 2019). A high prevalence of refractive errors (46.4%), squint (32.2%) and optic atrophy (32%) has been noted in children with CVI (Pehere et al., 2018). In the current study, only 4 children (3.6%) with CVI were using spectacles despite 40% (i.e., n=14/35) of the children who were examined having refractive error beyond age-norms and 85.4% (i.e., n=53/62) squint. The refractive error assessment was only carried out in a small proportion of children, as only a few parents could bring their children for the comprehensive eye evaluation (n=37, 33.3%). Of those who were examined, approximately 90% of the children had some form of refractive correction and 40% (i.e., n=14/35) were prescribed glasses post cycloplegic refraction. Future research

investigating the barriers to uptake of eye care services and spectacle usage in children with CVI is needed for understanding the reasons for above mentioned findings. In a retrospective longitudinal analysis carried out by Jimenez-Gomez et al, the neurologic, developmental and ophthalmic predictors responsible for improvement in CVI grade were determined. Refractive correction and rehabilitative therapies were noted to yield the maximum benefit in children with CVI (Jimenez-Gomez et al., 2022).

Hypoaccommodation has been noted to be high in children with SEN, such as cerebral palsy (57.6%) and was noted to be significantly associated with cognitive impairments ($p<0.01$) and severe motor delays ($p=0.001$) (McClelland et al., 2006). It is a well-established finding in children with DS (Nandakumar & Leat, 2010; Satgunam et al., 2019). In the current study, although amplitude of accommodation was planned to be measured it could only be assessed in 4 children due to time constraints. As the testing distance was 55 cms or less for all the tests, the amplitude of accommodation could influence visual functions estimates. The importance of including an accommodative component as part of the optometric management for children with DS has been emphasized, as poor accommodation can result in poor acuity particularly at near (Nandakumar & Leat, 2009). However, in a study carried out by Satgunam et al, near visual acuity was not found to be a sensitive indicator for hypoaccommodation in children with DS, indicating a greater need to perform dynamic retinoscopy(Satgunam et al., 2019). Poor accommodation has been well established in children with CVI as well (Pehere et al., 2018; Saunders et al., 2008). As the amplitude of accommodation was not measured on all children in the current study, we have acknowledged this as part of the study limitations. However, it is important to assess this parameter in future studies carried out on children with CVI and also in children with other SEN. Planning a battery of tests for children with SEN can prove challenging, particularly if planned on the same day. Therefore it is recommended to have the flexibility of running the tests on different days or sessions.

Oculomotor disorders are also common in children with CVI. The most typical features included poor saccadic eye movements (93%), variable angle squint (86%) and paroxysmal ocular deviations (78%) (Salati et al., 2002). In children with CVI, therapies targeting visual skills, such as visual attention, visually guided reach and various oculomotor abilities were noted to be beneficial (Delay et al., 2023). In a retrospective review of medical records (n=170) carried out by Huo et al, the most common associated ophthalmological abnormalities were esotropia (18.8%), exotropia (18.2%), optic atrophy (16.5%), nystagmus (11.1%) and retinal disease (3%) (Huo et al., 1999). In the current study, a higher proportion of children had optic atrophy (72.2%, 26/36), alternating exotropia (25.8%, 16/62), unilateral/bilateral exotropia (24.1%, 15/62) and unilateral/bilateral esotropia (22.5%, 14/62).

However, these were reported in a smaller sample of children who received comprehensive eye evaluation (n=36, 32.4%). The presence of nystagmus was noted to be higher in the current study (23.3%), indicating an intact striate cortex (Fielder & Evans, 1988) and concurrent anterior visual pathway defect (Huo et al., 1999). The higher proportion of children having optic atrophy in our study indicates the severity of hypoxic ischemic insult to the brain (Huo et al., 1999). As secondary optic atrophy can occur as a result of retrograde trans-synaptic degeneration in CVI (Uggetti et al., 1997), clinicians must carefully assess this abnormality in children with CVI. The presence of optic atrophy in CVI also implies poor prognosis (Huo et al., 1999).

Brain imaging

In the current study, most children were categorized into the moderate to severe brain damage group (n=19, 63.3%) among those whose brain imaging was graded (27%, 30/111). Optic radiations (82.8%) was noted to be the most commonly affected location, followed by white matter signal (79.3%), occipital lobe/visual cortex (69%) and white matter reduction (66.7%). Our study findings are in agreement with Cioni et al's study, in which multivariate analysis revealed the strong association between the severity of vision impairment and damage to the optic radiations.

Magnetic resonance imaging is widely used for determining structural defects of the brain in children with neurological vision impairments (Philip et al., 2020), only in few children there may be no identifiable abnormalities, but morphometrically abnormalities could be detected (Ortibus et al., 2009). The brain imaging scans indicating damage to the visual cortex, especially to the optic radiations can be considered as referral parameters for vision assessment which may need to be followed up longitudinally (Cioni et al., 1996). Earlier studies have focused on studying the imaged films and retrospectively graded the severity of the condition (Philip et al., 2020). This could have limitations such as unable to view the brain structures in real-time, study the structural abnormalities in greater detail and thereby the grading may be covering only gross aspects of the structures. Therefore, future studies using advances in MRI (such as diffusion tensor imaging (DTI) (Jones, 2008), high angular resolution diffusion-based imaging (HARDI) (Bauer et al., 2014)) will be useful to understand the extent and location of the brain damage in the CVI cohort. This would not only help in planning vision rehabilitation therapies alone, but therapies targeting other developmental areas as well (Philip et al., 2020).

7.3 Validation of visual acuity tools

Testability

Good testability rates[22] have been noted in our study using the VA tests in children with CVI (TAC-II=95.94%, PV app=82.88%) and in typically developing children (TAC-II=100%, PV app =100%). However, higher testability rates were observed in our preliminary study on children with Down syndrome (97.2%), which could primarily be due to better eye-hand coordination and also relatively older age. Grating acuity is less challenging when compared to conventional recognition acuity charts with optotypes such as letters, numbers, symbols and pictures and is therefore widely used in children with developmental delay (Sumalini & Satgunam, 2022). TAC-II has been used in infants and young children in earlier studies and its testability varied from approximately 50% in monocular testing to close to 99% in binocular testing (Sumalini & Satgunam, 2022). Peekaboo Vision app, which is a relatively new test was also noted to have good testability in typically developing children and in those with vision impairment (study 1: 93.6%, study 2: 94.9%) (Livingstone et al., 2019).

Reduced testability (approximately 12% lower) using the PV app in comparison to TAC-II in our study may be attributed to the following reasons: smaller screen size of the tablet when compared to the size of the card (in TAC-II), this could have distracted the child due to background visibility which was obvious with the tablet. The size of the screen could also potentially affect the relative placement of the gratings on the screen from the other blank side and is likely to elicit a smaller eye movement to look at the grating, thereby making it more challenging for the examiner to make a judgement about the child's eye movement in comparison to a larger eye movement with a 'bigger' card. Unfortunately, our study did not use eye tracking to quantify the eye movements which would have added more objectivity to the assessment and this lack of eye movement quantification may have contributed to approximately 19.3% of children being placed into the 'no engagement' group in the PV app in comparison 10.3% with TAC-II.

Engagement scores and order of testing

The engagement score of 2 (i.e., complete engagement) was fairly similar for TAC-II (30.1%) when compared to PV app (26.8%) in children with CVI and comparable for controls (TAC-II and PV app, 96%). In an earlier study by Livingstone et al on typically developing normally sighted children and children with VI cohort, the engagement score of 2 using PV app binocularly was noted to be 62% (median age: 3.08 years) and 78.3% (4.5 years) in study 1 and 2 respectively (Livingstone et al., 2019).

[22] *Defined as the ability to complete the test on first attempt*

Discussion

In the current study, the median age of children who were scored as having an engagement score 2 with PV app was 3.41 years (26.8%) and 3.0 years (90%) for children with CVI and controls respectively. Although a smaller number of children had complete engagement in the CVI cohort compared to Livingstone et al's study (Livingstone et al., 2019), the median age was almost comparable. The primary reason for this difference could be attributed to the differences in the characteristics of children in the current study (CVI) and Livingstone et al's study (typically developing normally sighted children and children with VI cohort) and to the subjectivity of the scoring itself.

Engagement scores are not commonly used in studies, the preference is to use testability rates as a surrogate measure. However, both are different. A child maybe testable but can lose interest in the middle of the test and not reach convincing threshold as ascertained by the examiner. It should however be acknowledged that engagement scores and testability are both subjective and likely to vary primarily based on the child's functioning level (Coulter et al., 2015) and also based on the examiner. In clinical set-ups, often examiners note down the reliability of the test result (for e.g., 1 CPD with 70% reliability), which is also very subjective. Using both engagement scores and testability method allowed us the opportunity to gain both perspectives as a means of gaining a more rounded picture of the validity of VA tests in children with CVI.

A significant difference in engagement scores based on the order of testing was found using the PV app but not with TAC-II. The engagement score with PV app as the first test was relatively better (complete engagement=37%, partial engagement=55.5%) as compared to when the app used as the second test (complete engagement=15.1%, partial engagement=60.6%). This maybe due to the limited attention span in children which is likely to be further restricted in children with SEN, such as in CVI. Lack of interest when looking at a black and white grating stimuli grating may also be a challenge in these children (Suttle, 2001), which is applicable to both PV app and TAC-II in the context of the current study. Therefore, in a clinical setting it is important to record acuity when the child is most active to get better engagement during the testing procedure.

Testing time

The testing time in our study was found to be comparable using TAC-II and PV app in children with CVI. However, the PV app was found to be faster in the control group. As discussed earlier (see section 5.6.5), the thresholding paradigms for both the tests are different. An automated staircase method was used by the PV app which should have ideally resulted in a shorter testing time when

compared to TAC-II, similar to controls for children with CVI. However, this was not the case. In order to respond by touch to the PV app testing, some children with poor eye-hand coordination were unable to use a single finger to touch the grating and placed their entire palm on the screen, which may have resulted in areas outside the grating being touched as well in some instances. This type of response would be registered as incorrect further prolonging the testing time due to the 3-up and 1-down staircase thresholding.

The testing times in our study in children with CVI (2.23±1.17 minutes) were shorter compared to an earlier study carried out on older children with SEN (3.4±1.85 minutes) using TAC-II. Although the earlier study also assessed binocular visual acuity, it included a group of different causes of special educational needs, such as CHARGE syndrome, spastic diplegia etc (Johnson et al., 2009) and did not include children with CVI. Although it is likely that the difficulties faced by both cohorts in terms of restrictions and cognition are likely to be similar (Jasper & Philip, 2018). It is possible that the differences found are largely down to the experience of the examiners and the testing environments.

The testing time in a group of normal infants (5-24 months), demonstrated that both binocular and monocular assessments can be carried within 2 to 5 minutes using TAC-II (Qiu et al., 2011) and our findings for both children with CVI (2.23±1.17 minutes) and controls (1.44±0.64 minutes) fall within this range. The testing time with the PV app was noted to be about 3.08 minutes in typically developing children and those with vision impairment and this was found to be about 1 min shorter in comparison to the Keeler acuity cards (Livingstone et al., 2019). This was analysed only in children who could be tested upto convincing threshold, which could be the possible reason for the longer testing time when compared to our study that included all the engagement categories (testing time, CVI: 2.24±0.98 minutes and controls: 1.23±0.51 minutes). The testing time per card comparison *(as reported for tests of CS-see section 6.4.1)* between tests of VA could not be carried out due to difference in their thresholding paradigms. Testing time per card gives an understanding of the actual time differences between the tests and among the groups of children, as thresholding time for those children who have poorer acuity could be shorter (for e.g., 2 or 3 cards) versus children who have better acuity and may take time for thresholding as all 15 cards may have to be presented.

Visual acuity

Summary table 7.1 provides comparison of key findings between TAC-II and PV app measurements in children with CVI and in controls. In our study, the range of acuities were noted to be wider for children with CVI: TAC-II= 0.19 to 2.3 logMAR and PV app= -0.18 to 2.2 logMAR and as expected

narrower for the control group: TAC-II= -0.12 to 1.55 logMAR and PV app= -0.18 to 0.9 logMAR. It should be noted that VA is likely to be 'changeable' in this age group even in normal children due to changes in visual function during the early years of life as part of normal visual development. We know that in terms of VA there is rapid development until 1 year of life with slower development from 2.5-3.0 years and finally stabilizing at 3 years of life in typically developing normally sighted children (Shi et al., 2006). However, children with CVI can have a spectrum of visual functioning, i.e., ranging from better acuity to extremely poor acuity levels (Pehere & Jacob, 2019).

The acuity estimates obtained in our study were in agreement with our preliminary study 2 (see section 5.6.3) comparing both these tests on children with DS and controls in relatively older children (chronological age range: 18 months to 17 years) (Sumalini et al., 2022). Only 18 children (18.3%) with CVI in the current study were within the 95% prediction limits of Leone et al's study (figure 6.5) Leone et al. (2014) carried out on typically developing children based on the chronological age. A majority of children were high functioning (phase III, n=15 (83.3%)) and a small number from the moderate functioning group (phase II, n=3 (16.6%)). Whereas 5 children (10%) from the control group also had poorer acuity than the lower limit prediction. These children were in the younger age group, i.e., 6 months to 1.83 years and the poor acuity could be likely due to poor concentration during the test procedure, as all of them were scored as having 'partial engagement'. All of them were from children's home and re-assessment is planned for any clinical care that maybe needed.

Significantly different mean acuities were noted in both groups using both the tests. Some of the differences observed between the two tests may be related to their thresholding paradigms. For TAC-II, the descending method of limits was used to present stimuli and responses obtained two out of three times were used to estimate grating acuity. The procedure is manual and not automated as in the PV app (3-up and 1-down). In case of children who give consistently correct responses, the acuity could be thresholded faster when compared to TAC-II. However, the testing times in our cohort was only shorter with PV app for controls when compared to TAC-II. It was comparable in children with CVI. All the children were encouraged to indicate the grating location for both tests, however, some could not do so because of motor issues, poor eye-hand coordination (visually guided reach) and also because of unwillingness, due to which the PI had to make a judgement based on the eye movement of the child. As discussed earlier, the challenge of judging the response by the examiner accurately can also be speculated as one of the reasons for the difference in the acuities, primarily due to the different size of the screen vs. the card (see section 7.3 on testability). The other reasons could be the step size differences that was discussed in our preliminary study 1 as well. The narrowest LoA between both

tests was noted in the older children (>5-7 years) in the control group (i.e., 95% LoA: -0.33 to 0.17 logMAR, mean difference: -0.08±0.13 logMAR). However, similar findings were not noted in the older children with CVI. Peekaboo Vision app has larger step difference towards the higher spatial frequency (i.e., 0.12 to -0.18 logMAR), resulting in a 0.3 logMAR jump. The other reason could be due to the difference in the nature of the tests, i.e., electronic display (in PV app) vs. card-based (TAC-II). Some children (particularly those with better acuity as their thresholding takes longer time) may have lost interest during the mechanical changing of cards when compared to focusing on the electronic screen with the cartoon in case the child gave the correct response. The luminance of the target varies between tests that are card-based vs. electronic display, this also could be another factor responsible for the difference in the acuity estimated between both the tests (Livingstone et al., 2016). Livingstone et al previously demonstrated the use of the iPad as suitable VA assessment tool, conforming closely to the ETDRS photometric compliance (Livingstone et al., 2016). However, no luminance measures were reported in Livingstone et al's study comparing acuity estimates using the PV app and Keeler acuity cards (Livingstone et al., 2019). In the current study, the luminance between the tools ranged from mean value of 72±9 cd/m^2 for TAC-II vs. 153±8 cd/m^2 for the PV app. Ceiling effect was noted only in 3 children (3.75%) with the PV app in the current study and none with TAC-II in children with CVI, however, floor effect was noted in 8 children (10%) with the PV app and 20 children (20.4%) with TAC-II. The testing distances used for TAC-II included 38 cms, 55 cms and 84 cms as per the recommended guidelines. For the PV app, the testing distance range that was available was from 25 cms to 50 cms. The exact distance was chosen keeping the child's arm length in mind and measured accordingly and set at that distance. Accommodation disorders which are reported to be present in children with CVI, could also play a role at such close testing distances. However, amplitude of accommodation could not be measured for all children as part of this study.

An earlier review (Mackie & McCulloch, 1995) that was published about a quarter century ago summarizes the acuity estimates using acuity card procedures and following the preferential looking paradigm (see table 2.3). A previous study carried out on individuals with special educational needs which included different multiple sensory, motor and/or cognitive impairments, not very dissimilar to the current study's cohort found TAC-II and Cardiff acuity cards to be similar (p=0.068) (Johnson et al., 2009). However, age ranges (5-21 years) were higher when compared to the current study (mean:3.0±1.85 years, range: 7 months to 7 years), which is likely to result in comparable results between the VA tests and account for differences between the two studies.

Discussion

In a separate study carried out on younger children with and without vision impairment, comparable VA was reported using PV app and Keeler acuity cards within the age range of 6-60 months (mean acuity difference, study 1= 0.02 logMAR, 95% LoA=0.33 to 0.37 logMAR; study 2= 0.01 logMAR, 95% LoA=-0.413 to 0.437 logMAR) (Livingstone et al., 2019). The 95% LoA between TAC-II and the PV app obtained in our control group (-0.72 to 0.44 logMAR) was noted to be wider when compared to Livingstone et al's study, despite the minimum age being similar in both studies (i.e., 6 months). Few of the reasons could be attributed to the differences in study settings, experience of children in using the electronic devices and PI clicking it for the children when touch response was not possible by the child. Neu et al underlines the differences in stimulus configurations between TAC (no defined edges) in comparison to Keeler acuity cards (circular edges for both grating and blank side), in addition to the differences in spatial frequencies and step sizes. However, the study reported comparable monocular acuity estimates (i.e., 84.2% were within 0.5 octave difference) among normally sighted children aged 7 months to 6 years (Neu & Sireteanu, 1997). In the current study, TAC-II was used due to which the 'edge artefact' is not applicable (Clifford et al., 2005).

The VA estimates obtained in children with CVI (-1.03 to 0.53 logMAR) was wider when compared to both our control group and Livingstone et al's study which could be clearly due to the multiple delays in children with CVI (i.e., motor, cognition and poor attention). These LoA were relatively wider when compared to the acuity limits obtained using PV app and Keeler acuity cards (study 1: 0.33 to 0.37 logMAR, study 2: 0.413 to 0.437 logMAR) (Livingstone et al., 2019). In the current study, the differences in the mean acuities varied based on the chronological age categories in children with CVI. Interestingly children in the younger ages group (n=9, mean difference: -0.02±0.34 logMAR, 95% LoA: -0.68 to 0.64 logMAR) had smaller VA difference when compared to older children (n=14, mean difference: -0.57±0.35 logMAR, 95% LoA: -1.25 to 0.11 logMAR). Some reasons could be that for very young children it is likely that the examiner made the decision on both tests which could result in parity. Also, very young children have poorer acuity and there is not much difference because of closer step sizes at the lower spatial frequency between TAC-II (2.3 logMAR) and the PV app (2.11 logMAR). However, the same trend was not observed in younger controls but due to very small sample size (n=4), conclusions could not be drawn effectively.

The commonality in both these studies (Johnson et al., 2009; Livingstone et al., 2019), is the comparison of a grating acuity test vs either vanishing optotypes (Cardiff acuity cards) or an automated grating (PV app), but all of these tests using preferential looking technique. It is important to note from the current study that the PV app over-estimates VA in comparison to TAC-II in both

groups of children (0.25 logMAR in CVI and 0.14 logMAR in controls). On the contrary, it could also be argued about the underestimation of acuity by TAC-II mainly due to the attention component. Teller acuity cards-II lack interactive feedback features (both visual and auditory) which are both available on the PV app. This lack of interactive feedback may have a negative effect on participants' attention skills. Weiss et al's study on infants who were visually unresponsive during clinical examination were evaluated to have normal VEPs and acuities were noted to be within age-normative range categorized based on established TAC normative data and were diagnosed with visual inattention(Weiss et al., 2001). This underlines the importance of visual attention on visual function measurements in infants and young children. However, this component is often not quantified in the clinic.

There are two implications for this difference in acuity measurements, given the wider LoA between both tests, it is very important to note down the test being used in the clinical assessment and ensure to continue using the same test at follow-up visits for better interpretation of the change in acuity measure if any during the visits. Secondly, age-normative data is needed for appropriate clinical interpretation for both tests and condition-specific acuity estimates, for e.g., in children with SEN who present with multiple developmental limitations. We were able to provide the VA estimates for children with CVI in the current study (table 7.1) and for DS in the preliminary study 2 and compare against the gold-standard TAC-II. However, future studies will be needed to determine the age-normative data for children with different causes of SEN, as the conditions are heterogeneous.

Determining the examiner bias was done through the video analysis of a random sample in the current study (see section 6.3.2). Although an in-person judgement of examiner 2 would have been appropriate to understand this bias better. In the current study, video analysis was deemed appropriate in place of in-person observation due to logistical reasons, such as partial lockdowns and restrictions imposed due to the pandemic. Therefore, in the current study, videos were recorded and video analysis was performed by an experienced examiner who was masked (except to the thresholding that was obvious in the video) to the readings of the PI. This exercise was primarily carried out to understand any examiner bias caused by the fact that the cards were placed sequentially in a descending order of limits. The difference between examiner 1 and 2 was noted to be small (0.01±0.07 logMAR and 95% LoA: -0.13 to 0.15 logMAR with CR of 0.12 (n=30)) and this was only done for the first measurement of TAC-II. However, it must be acknowledged that the post-hoc analysis meant that, the judgement of second examiner would likely be influenced by the judgement of PI. Due to this limitation, the second examiner was questioned as to whether they would agree with examiner 1 or stop the assessment at an

earlier or later stage. For 5 children with CVI (16.6%), examiner 2 responded that they would have ended the testing 1 card before what was recorded by the PI.

	CVI		**Controls**	
	Teller acuity cards-II 	**Peekaboo Vision application** 	**Teller acuity cards-II** 	**Peekaboo Vision application** 
Testability rate	95.4%	82.8%	100%	100%
Engagement score-complete	30.1%	27.1%	90%	90%
Mean testing time (minutes)	2.23±1.17	2.24±0.98	1.44±0.64	1.23±0.51
Mean visual acuity (logMAR)	1.46±0.64	1.05±0.68	0.3±0.4	0.16±0.3
Range of visual acuity (logMAR)	0.19 to 2.3	-0.18 to 2.2	-0.12 to 1.55	-0.18 to 0.9
Mean difference of acuity (logMAR)	-0.25±0.40		-0.14±0.30	
95% limits of agreement (logMAR)	-1.03 to 0.53		-0.72 to 0.44	
Coefficient of repeatability (logMAR)	0.47	0.99	0.27	0.41

Table 7.1: Summary of key findings of the study using Teller acuity cards-II and Peekaboo Vision application

7.4 Validation of contrast sensitivity tools

Testability

The testability rates were found to be slightly higher with HH cards (91.89%) when compared to OCC (89.18%) in children with CVI. In the control group, both the tests were noted to have 100% testability. Hiding Heidi cards are commonly used to measure CS in the paediatric age group. The face stimuli in HH cards may have been relatively appealing to children when compared to the grating stimuli in OCC, resulting in better testability rates. In an earlier study carried out in normal children aged 1-8 years, HH cards demonstrated excellent testability of 96.66% (Leat & Wegmann, 2004). The OCC were also found to have good testability (90%) in school-aged children with vision impairment (Osman et al., 2021), very similar to our cohort of children with CVI.

Discussion

Engagement scores and order of testing

The order of testing had no effect on the engagement scores for both HH cards (p=0.86) and for OCC (p=0.7) in children with CVI. The engagement scores were noted to be comparable between OCC and HH cards in children with CVI (table 6.16). Whereas in controls, the HH cards had better engagement scores when compared to OCC. This could be attributed to two reasons. Firstly, the perception of the saliency of face (as in HH cards) vs. grating (as in OCC) may not have been very different for children with CVI considering their visual perceptual concerns. Children with CVI can have prosopagnosia(Dutton, 2013), However, this was not evaluated as a part of this study. Also, the OCC has 12 levels of contrast assessment when compared to 6 levels in HH cards that may distract the child from being focused throughout the testing procedure, which was apparent in the total testing time differences between both CS tools (in children with CVI and in controls, $p<0.01$, Wilcoxon).

The 'complete engagement scores' in children with CVI were noted to be slightly better for tests of VA (TAC-II: 30.1%, PV app: 26.8%) when compared to tests of CS (HH cards: 21.5%, OCC: 22.2%). The visual functions testing was randomized, with exception of the PV app being presented as the first test for children who were not cooperating at the start of the test (n=10) in order to pacify them by showing an electronic device in place of card-based tests. However, the other reasons for the slight differences in engagement scores for tests of VA and CS is unclear.

Testing time

The testing times were significantly shorter using HH cards in comparison to OCC (in both children with CVI and controls). As mentioned earlier, this could be confounded by a smaller number of contrast levels assessed using HH cards when compared to the OCC. In order to look into this further, we tried analysing the time per card for both the tests and found that there were no significant differences in children with CVI (p=0.07) and in the controls (p=0.59). Our study findings note relatively longer testing time using OCC (1.23±0.66 minutes) in children with CVI when compared to a previous study using OCC on individuals with vision impairment (1.06±0.61 minutes, aged: 10-20 years), comparable to the gold standard Pelli-Robson contrast chart (0.95±0.53 min) (Osman et al., 2021). This could be because of the differences in the study cohorts. In a recent study on a small sample of children with CVI (n=20), the total testing time range was between 2-3 minutes with a face stimulus-based CS tool called the Mayer-Kran double happy low contrast test in children aged 2-18 years. This is a picture-based contrast test similar to HH cards and assess 15 levels of contrast (Mayer et al., 2020) and therefore could result in longer testing time.

Contrast sensitivity

Summary table 7.2 provides comparison of key findings between HH cards and OCC measurements in children with CVI and in controls The CS values obtained in our study using HH cards and OCC for children with CVI was found to have wider LoA (95% LoA: -0.37 to 0.49 logCS, mean difference: 0.06±0.22 logCS) as expected when compared to that of controls (95% LoA: 0.06 to 0.49, mean difference: 0.27±0.1 logCS). However, significantly different mean CS values were noted in both groups using both the tests ($p<0.001$). The differences in the contrast levels that can be assessed between both tests and the sizes between one contrast measurement to another within the same test could be the reasons for these difference in the CS values. In the current study, 53 (54.6%) and 35 (37.6%) children were noted to have floor effect using HH cards and OCC respectively among children with CVI and none in the control group. This was apparent in the small mean difference (0.06±0.22 logCS) between the tests in children with CVI, as a sizeable number of children had poor contrast sensitivity when measured using both CS tests. These differences can be mainly attributed to the step sizes that these tests can measure, for e.g., in HH cards, the contrast value after 100% contrast card (least difficult card) is 25%, followed by 10%, 5%, 2.5% and 1.25%. The CS values between 100% to 25% did not get captured using HH cards that may have resulted in higher children with CVI having floor effect (54.6%) when compared to OCC (37.6%). However, OCC has 12 different levels of contrast that can be assessed: 100%, 71%, 50%, 35%, 25%, 18%, 12.6%, 8.9%, 6.9%, 4.5%, 3.0% and 2.2%. Having multiple step sizes are desirable in assessing persons with vision impairment and also in CVI, as they could have varied CS levels (Good et al., 2012; Hyvarinen, 1983) unlike normally sighted children. It would be interesting to see whether different tests measuring similar/near similar contrast levels would yield comparable or variable results in different groups of children. Also, very young children with CVI had lesser difference between the tests (-0.01±0.23 logCS) when compared to the older children. This essentially is due to the poor CS in the younger age group and therefore majority of the children touching the floor effect with both tests.

In the current study, it was noted that OCC under-estimated the CS when compared to HH cards by 0.06 logCS in children with CVI and by 0.27 logCS in typically developing children. A ceiling effect was noted only in 5 (5.1%) and 6 (6.4%) children with HH cards and OCC respectively among children with CVI. Whereas a ceiling effect was noted among 42 (84%) and 34 (68%) children with HH cards and OCC among the controls. The HH cards can measure CS up to 1.9 logCS and OCC can quantify up to 1.66 logCS, this difference could have caused a higher mean difference between both tests in controls (0.27±0.1 logCS) when compared to children with CVI. Leat et al's study on typically

developing children (aged 1 to <8 years) revealed that all the children had a ceiling effect using HH cards (Leat & Wegmann, 2004). The difference in the CS values could also be attributed to the different nature of the stimuli. In the case of HH cards, the spatial frequency of different parts of the stimulus are different. For example, the outline of the face (~3.0 CPD) has a much lower spatial frequency when compared to the fine details such as the diameter of the centre eyeball (~ 9 CPD) (Chen & Mohamed, 2003). This task is more of a detection task than that of resolution (Leat & Wegmann, 2004). Ohio contrast cards also uses very low spatial frequency (0.15 CPD), but the difference is that these levels are fixed across all the contrast levels (Hopkins et al., 2017). In Leat et al's study, the CS values obtained using HH cards and Pelli-Robson chart were found to be significantly different among typically developing children aged 6 to < 8 years and in young adults (23-37 years) (Leat & Wegmann, 2004). Contrast sensitivity measures using OCC on the other hand were found to be comparable with Pelli-Robson chart among school-aged children with vision impairment (age:7-20 years, 95% LoA was OCC: ±0.42 logCS and Pelli-Robson: ±0.51 logCS) and among elderly cohort (age: >65 years, 95% LoA was OCC: ±0.27 logCS and Pelli-Robson: ±0.28 logCS) (Osman et al., 2021).

A comparison of CS tests among SEN cohort is limited. In the high and 2.5% low contrast acuity assessment among children with cerebral palsy and DS (aged 4-18 years), the mean acuity difference was noted to be 0.4 logMAR (95% LoA:±0.22 logMAR) (Little et al., 2013). Keeping in view the significantly different CS values, as noted in the current study, it is best not to use different tests interchangeably for appropriate interpretation of the change in the CS. While having finer step sizes helps in capturing contrast levels closer to the child's actual visual functioning capacity, it is important to consider the purpose of the test also, for e.g., it is not mandatory for a screening test need to measure finer step sizes, but it is desirable to have shorter testing time. The Ohio contrast cards seem to be a promising tool for both clinical and research purposes for finer step size assessment and better repeatability as determined in this study. Whereas HH cards were primarily developed for the preverbal and non-verbal groups of infants and children. No specific testing distance has been recommended for this test, but rather it is suggested to determine the test distance at which the child is able to respond to the Heidi's face and to use this for day-to-day visual communication. The primary purpose of these cards is to get easy and meaningful CS information for suggesting contrast enhancing measures for day-to-day interaction (Hyvarinen, 2018a), (for e.g., suggesting to use contrasting toy as compared to the background).

Discussion

Several studies indicate that CS is a sensitive measure and relates closer to real-world functioning than other visual functions (Jindra & Zemon, 1989; Stalin & Dalton, 2020; Thomas et al., 2020). In the current study, only 8 children with CVI (8.4%) had CS estimates within 95% confidence intervals of the controls (figure 6.8) and they were all noted to be in the high functioning cohort (phase III) and were also noted to have VA ≤0.67 logMAR. It is also important to note that in children with CVI, CS can be a sensitive measure (Good et al., 2012) and needs to be included as part of the regular clinical protocol. In our current study, we noted that relatively higher proportion of children touched the floor effect in CS test (OCC, 37.6%), when compared to acuity test (TAC-II, 20.4%). This implies that CS maybe affected in such children despite having relatively better acuity, similar to some ocular causes of vision impairment (Alahmadi et al., 2018; Jindra & Zemon, 1989), where CS was found to be useful to diagnose the conditions early on even before acuity loss is noted. In children with CVI as well, CS was noted to be more affected than VA when studied using electrophysiological techniques (Good et al., 2012). Further studies are needed to understand this trend in children with CVI using behavioural techniques.

	CVI		**Controls**	
	Hiding Heidi cards 	**Ohio contrast cards** 	**Hiding Heidi cards** 	**Ohio contrast cards** 
Testability rate	91.8%	89.1%	100%	100%
Engagement score-complete	21.5%	22.2%	100%	82%
Mean testing time (minutes)	0.95±0.56	1.23±0.66	0.53±0.38	1.01±0.83
Mean contrast sensitivity (logCS)	0.48±0.62	0.42±0.54	1.00 to 1.9	0.74 to 1.66
Range of contrast sensitivity (logCS)	0.00 to 1.9	0.00 to 1.66	-0.12 to 1.55	-0.18 to 0.9
Mean difference of contrast sensitivity between Hiding Heidi and Ohio contrast cards (logCS)	0.06±0.22		0.27±0.1 1	
95% limits of agreement between Hiding Heidi and Ohio contrast cards (logCS)	-0.37 to 0.49 logCS		0.06 to 0.49	
Coefficient of repeatability (logCS)	0.55	0.24	0.27	0.08

Table 7.2: Summary of key findings of the study using Hiding Heidi cards and Ohio contrast cards

7.5 Repeatability of visual functions

Visual acuity

The test-retest repeatability according to clinical protocols is normally considered to be 2 lines of the logMAR chart in recognition acuity (Beck et al., 2003). However, octaves are used commonly to refer to test-retest differences in resolution acuity tests (Mackie & McCulloch, 1995). The difference between 1 card to the other in TAC-II is equal to 0.5 octave (Teller et al., 2005 (revised)). Several studies reporting grating acuity use 1-octave difference (i.e. 2 cards) as the acceptable range for test-retest variability in typically developing children and in some groups of children with developmental delays (Mackie & McCulloch, 1995). The review paper (Mackie & McCulloch, 1995) summarizes the different grating acuity measures used by several studies such as the acuity card procedure following the operant or forced-choice preferential looking paradigms and also electrophysiological techniques such as VEP in typically developing children and those with SEN (such as preterm babies with developmental delays, cerebral palsy, DS) (see table 2.1). In our study, we used 2 tests following the 2-AFC preferential looking paradigm (i.e., TAC-II and PV app). As expected, repeatability was found to be better in typically developing children when compared to children with CVI. Our results indicate that TAC-II has better intra-observer repeatability when compared to PV app in both children with CVI and in the typically developing children. In the current study, 76.2% and 50% of children with CVI had acuity within 1-octave test-retest difference using TAC-II and PV app respectively. Our study findings of the repeatability indices of TAC-II (i.e., 76.2% within 1-octave) is in agreement with the earlier studies carried out on children with heterogenous causes of special educational needs (67-73%, aged: 6 months to 19 years) (Schenk-Rootlieb et al., 1992), cerebral palsy (76%, aged; 2-7 years) (Hertz & Rosenberg, 1988) In the study carried out on older aged children (5-21 years, n=21) with multiple sensory, visual, auditory, motor and/or cognitive impairments, the repeatability of acuity recorded using TAC-II was between ±0.6 logMAR. In our controls, 93.7% and 68.7% had acuity within 1-octave test-retest difference using TAC-II and PV app respectively.

Peekaboo Vision app is a relatively new test. The test-retest measures are reported for typically developing normally sighted children with and without vision impairment (CR=0.27, study 1; CR=0.32, study 2) (Livingstone et al., 2019), by our group in children with DS (CR=0.35) albeit in a very small sample (Sumalini et al., 2022) and in the current study we note a CR of 0.99 and 0.41 for children with CVI and for controls. These values indicate that there is a test-retest difference of approximately 9.9 lines and 4.1 logMAR lines in children with CVI and controls respectively. Although it is reported in a small sample in our study (n=16), it is important to consider this test-retest difference for appropriate clinical interpretation while using the PV app.

Discussion

In the current study, the test-retest mean differences was noted to be 0.06±0.36 logMAR with 95% LoA: -0.64 to 0.76 logMAR in children with CVI and mean difference: 0.01±0.22 logMAR with 95% LoA: -0.42 to 0.44 logMAR in controls. This was noted to be wider when compared to Livingstone et al's study, mean acuity difference: -0.042 logMAR, 95% LoA was -0.283 to 0.198 respectively in study 1 and mean acuity difference: -0.012 logMAR and 95% LoA: -0.344 to 0.32 logMAR with PV app in study 1 and 2 respectively. (Livingstone et al., 2019). Few of the reasons could be attributed to the differences in study settings and experience of children in using the electronic devices. The acuity using the PV app is measured at 0.1 logMAR intervals, except at the finest resolution where there is a jump of 0.3 logMAR (for e.g., 0.12 to -0.18 logMAR). This could also have been one of the reasons for the test-retest variability in controls (Sumalini et al., 2022) and in some children with CVI having good acuity. One of the other reasons could be the nature of the task, some children with CVI and most of the controls attempted to touch the screen to register the response. Due to their poor eye-hand coordination (in children with CVI), there is a possibility for the children to incorrectly touch the screen although they could have detected the grating correctly. This could have led to an incorrect response.

Contrast sensitivity

In the current study, we note that the repeatability indices of OCC were excellent for both children with CVI (95% LoA: -0.19 to 0.18 logCS, CR: 0.24) and controls (95% LoA: -0.07 to 0.11 logCS, CR: 0.08), when compared to HH cards in both cohorts (CVI: 95% LoA: -0.47 to 0.39 logCS and controls: -0.26 to 0.32 logCS, CR: 0.27). This could be most likely attributed to the closer step-sizes in both the cards at lower threshold values. The 95% LoA of the test-retest repeatability of CS using the well-established Pelli Robson chart was found to be ±0.51 logCS for low vision school aged-children when compared to OCC (±0.42 logCS) (Osman et al., 2021) were noted to wider when compared to our findings. The Spotchecks contrast sensitivity carried out on normally sighted children (4-12 years) were noted to have similar 95% LoA (-0.13 to 0.14 logCS) as that of repeatability indices noted in OCC in the current study in children with CVI. The effect of step sizes on the repeatability indices has been mentioned by Dougherty et al, in a study comparing MARS letter CS chart to Pelli-Robson CS chart. The MARS letter CS chart was noted to have better repeatability (95% LoA: ±0.13 logCS) when compared to Pelli-Robson CS chart (95% LoA: ±0.17 logCS) due to the closer step sizes (Dougherty et al., 2005) (each letter on MARS chart corresponds to 0.04 log units (Dougherty et al., 2005) and each letter on Pelli-Robson chart corresponds to 0.15/3=0.05 log unit approximately (Arditi, 2005)). Therefore, tests with smaller step sizes can be more repeatable when compared to those with larger jumps (Dougherty et al., 2005), as noted in our current study with OCC and HH cards. In HH cards,

after 100% contrast card the next jump is 25%. Hence a child who saw 100% earlier may also fixate to it in the next visit as well but may have missed the next card due to the larger jump. If there was a finer step size, there could have been reliable measures for repeatability. Hence caution should be applied in interpreting the result.

There is limited understanding of the repeatability indices of CS tests when compared to the acuity tools in the paediatric population. To the best of our knowledge, previous studies have not investigated the repeatability indices of HH cards. It is likely that children will respond easily to a face stimulus in HH cards, when compared to grating-based OCC. Despite the friendly stimulus and a smaller number of cards to test, the primary reason for lower repeatability indices could be attributed to unequal step sizes in the test. The next immediate level after the 100% contrast threshold is the 25% threshold and there are no intermediary steps that can be quantified. If child was not concentrating when the 25% card presented during a test/retest, the CS could be recorded at 100% and could give rise to a wide difference in the test-retest measures. This was more obvious in our cohort of CVI. A similar face stimulus test for CS assessment has been developed for children, called the Mayer-Kran Double-Happy test (Mayer et al., 2020). This test has 15 contrast levels that can be assessed (0.05 to 2.1 logCS). The inter-examiner variability in a cohort of children with ocular vision impairment (n=23) and with CVI (n=20), was found to be comparable (mean=-0.003±0.22 logCS; p=0.46, ICC: 0.921). The values obtained using Double-Happy test were noted to be marginally a better predictor of the diagnosis than VA (Mayer et al., 2020). Considering the various features of this test and the good inter-examiner variability, this test can be explored further and tested for its test-retest differences prior to using it in the clinical settings and research studies in children with SEN.

Through the current study, we understand that the test-retest differences are variable in children with CVI when compared to typically developing children for both VA and CS measures, although with a small sample size. The intra-observer repeatability indices revealed that TAC-II (1.5 octave[23] in children with CVI and within 1 octave in controls) had better repeatability when compared to the PV app (above 3 octaves in children with CVI and within 1.5 octave in controls). Therefore, it is not suggestible to use the tests of VA interchangeably. Ohio contrast cards (0.24 logCS in children with CVI and within 0.15 logCS[24] in controls) was noted to have better repeatability indices when compared to HH cards (0.55 logCS in children with CVI and 0.27 logCS in controls), thereby

[23] The difference between 2 adjacent cards is 0.5 octave in TAC-II and that of 2 cards is 1 octave

[24] The contrast of a triplet changes by 0.15 logCS in Pelli-Robson contrast sensitivity chart and also 0.15 logCS is the difference between 2 adjacent cards in OCC

suggesting not to use the CS tests also interchangeably. In children with CVI, this also indicates that CS (CR: 0.24 logCS) using OCC yielded within 2 cards repeatability and VA (CR: 0.47 logMAR) using TAC-II yielded about 3 cards repeatability (i.e., ~1.5 octaves).

The visual challenges in CVI can range from low to high functioning (Pehere & Jacob, 2019) and the repeatability indices are likely to differ in each group. Therefore, it is not ideal to generalize the results across the spectrum in CVI. A larger sample size will be needed to understand the repeatability measures of visual functions based on the severity of CVI.

7.6 Visual functions and associative factors

Functional vision

The CVI range instrument includes the 10 characteristics commonly present in children with CVI. As discussed earlier (see section 5.6), this instrument has 2 rating scales, namely the across-the-characteristic scale and within-the-characteristic scale. In this study, we only included the across-the-characteristic scale that gives us an overview of the child's functional vision performance. Whereas, within-the-characteristic scale helps us understand the effect of each characteristic on the overall score (Newcomb, 2010). We could only carry out the across-the characteristic scale, due to time constraints. The findings from within-the characteristic scale could have helped as to which characteristics are better associated with the visual functions. This could not be determined in this study and may need further research to understand.

Functional vision and visual concerns

Fourteen unique visual concerns were identified in children with CVI with the most common ones being difficulty in maintaining eye contact and recognizing faces. A previous study has also reported face recognition as one of the main concerns in children with CVI (Bauer et al., 2023). The significantly different frequency distribution of visual concerns across the 3 phases of CVI based on the functional vision score is an important finding. While children in phases I and II are likely to have concerns with less visually demanding tasks (such as face identification and maintaining eye contact), they were also noted to be ≤3 years of age. Whereas, those from phase III, mostly encounter issues with the more challenging tasks (such as missing objects on the lower or side field). In children who were above the age of 3 years, eye contact remained a concern followed by missing objects on the lower/side field. It is likely that very young children only perform less visually demanding tasks due to their age, such as recognising known people and smile and as they get older, they are more mobile and therefore undertake more challenging tasks such as explore the surroundings better. Also, it is easier

for parents to notice visual concerns in older children when compared to very young children, as they may not be aware of the age-appropriate visual milestones from very early on in life. But it becomes apparent as the child grows up. Similar visual concerns of difficulty in maintaining eye contact, recognizing faces and bumping into objects were reported by parents of children with various causes of SEN as discussed in our preliminary study 1 (see section 4.2).

More than one visual concern was more likely to be reported by parents of children belonging to phase I (n=12) and II (n=11) when compared to those from phase III (n=5). Children with poor eye contact, inability to recognize faces or look at or track lights were easily identified by the parents than less obvious concerns (for e.g., taking time to look at objects/people). Parent-reported visual concerns indicate the need for a detailed history taking. Clinicians usually have limited interaction with children, given the time constraints and as children are in a different environment, they may not be functioning visually to their full capacity (e.g., maintaining eye contact with clinician). Questioning the parents/caregivers, is important to record these visual concerns, plan the battery of tests accordingly to understand the concerns better and suitably address them.

Functional vision and visual functions

Functional vision assessment is often carried out in low vision rehabilitation centres and is specifically important in children with developmental delays. The functional vision in children with developmental delays could be very different due to interaction of delays in multiple areas, such as vision, fine motor, gross motor, cognition and speech and may not be fully explained by the ocular diagnosis alone. Children of parents who did not report any vision concern (phase III=5, phase II=1) had a range of acuity between 0.19 (close to normal) to 1.28 logMAR (moderate vision impairment) and CS ranging from 0.6 (reduced) to 1.66 (normal/near normal) logCS. This indicates that parents may not always be able to identify visual concerns in children with CVI even if their acuity and contrast are reduced. Developmental delays could make it harder for parents to notice visual problems. Therefore, parents of all children with CVI should be questioned about the child's functional vision problems as in some children these problems can be missed or not looked for. Upon questioning, parents will also be aware to look for those domains of functional vision.

In the current study, VA, CS and developmental age taken together are able to best predict the functional vision score of the child (78.4%). These findings indicate the importance of a functional vision assessment to understand the child's visual potential that forms the basis to devise suitable vision rehabilitation strategies. Several studies report the functional vision measure as an outcome

parameter to determine the effectiveness of any particular treatment or rehabilitation plan (Bullaj et al., 2022; Dale & Sonksen, 2002; Dale et al., 2019). A lot of subjectivity can exist in functional vision assessment due to unstandardized tools used for examination, varying test distances and no specifications to follow as in conventional acuity recording. However, a well-structured functional vision assessment protocol can be very helpful in understanding the visual difficulties faced by the child under real-world conditions. Salt et al demonstrated a well-structured functional vision assessment protocol in infants and toddlers with severe ocular vision impairment using the near detection scale. Quantifying the change in the functional vision was feasible using near detection scale when acuity is not otherwise measurable (Salt et al., 2020).

In the current study, there was a marginally higher correlation of CS and functional vision (r=0.86, r^2= 0.73) when compared to VA and functional vision (r= -0.83, r^2= 0.68). This could primarily be attributed to the 10-CVI characteristics (see appendix A14) which are more contrast-based than size/VA-based. Earlier studies also reported that CS is a sensitive measure to detect several ocular causes of vision impairment (Xiong et al., 2020) and in children with CVI (Mayer et al., 2020). This suggests that CS is a very important parameter to be captured in children with CVI.

On studying the mean differences between VA tests based on the CVI phase, there was a wider difference in phase II and III when compared to phase I. This could be attributed to the poor acuity in children within phase 1 due to which they were mostly restricted to the lower spatial frequency using both tests. However, with better functioning (CVI phase II and III), their ability to respond to both the tests was seen and noted to be variable, most likely due to the differences in the tests that have already been discussed (see section 7.4). Whereas, for tests of CS, phases I and II had lesser difference between the tests when compared to phase 3. These findings indicate that the high functioning children showed more variability between the tests, although their CS was significantly better (see table 6.23 and 6.24) than other 2 phases. This may also be due to the differences between the 2 tests that are discussed in section 7.4. These findings imply that clinicians should be mindful of the variability that could be higher with the high functioning group as their visual functions are better than the low and moderate functioning groups, but their general behaviour such as limited attention span may impact the findings. No studies have compared the agreement between the tests of visual functions based on the severity of CVI for drawing suitable comparisons with our study findings.

Developmental quotient/age

Several studies carried out on children with CVI had demonstrated moderate to strong association of developmental quotient/age to the visual functions (Cioni et al., 2000; Fazzi et al., 2021; Morelli et al.,

2022). The current study has similar findings in terms of the correlation between developmental age and VA (r=-0.51), CS (r=0.55) and functional vision score (r=0.71). It is important to note that the developmental assessment tools do not include a vision domain to the best of our knowledge although certain tasks in other domains are indirectly dependent on visual ability of the child. The implications of moderate to strong correlation in this study suggests that paediatric neurologists and developmental psychologists should refer the child for eye care and vision rehabilitation services. Similarly, eye care personnel should also cross-refer the child for detailed neurological and developmental assessments on suspecting CVI. The findings do not relate to cause-and-effect relationship, but only provide a correlation between these parameters.

Developmental age has better correlation with vision-related parameters, when compared to the chronological age. The developmental trend of both VA and CS was better explained by the developmental age (TAC-II: r^2=0.43, PV app: r^2=0.54, HH cards: r^2=0.54, OCC: r^2=0.66) when compared to the chronological age (TAC-II: r^2=0.2, PV app: r^2=0.36, HH cards: r^2=0.35, OCC: r^2=0.28). This finding was similar even for the functional vision score (developmental age, r^2=0.41; chronological age, r^2=0.26). Our findings suggest that the developmental quotient/age can serve as a referral parameter for developmental psychologists and neurologists for comprehensive eye evaluation and vision rehabilitation.

Seizure history

Seizures are one of the most common neurological abnormalities in children with CVI (Harding et al., 2002; Huo et al., 1999; Jimenez-Gomez et al., 2022) very similar to the findings of the current study (~80%). In a longitudinal follow-up study of children with CVI, it was found that those with a epilepsy history had a negative impact on the CVI grade (Jimenez-Gomez et al., 2022). Infantile spasms may damage optic radiations and/or visual cortex (Castano et al., 2000; Huo et al., 1999). Visual functions were noted to improve with controlled seizures activity (Good et al., 1994; Wong, 1991). However, antiepileptic medication, especially vigabatrin can to cause peripheral visual field loss (Harding et al., 2002). The current study did not investigate the effect of antiepileptic medication in these children, as this was beyond the scope of the research question. However, the current study findings reveal that children who had the last episode of seizure 3 months before had significantly better VA (using TAC-II), CS (using OCC) and functional score (using CVI range instrument) compared to those who had last episode within the last 3 months duration, similar to the findings by Wong (Wong, 1991) who noted that there were poor prognostic signs in terms of visual recovery in children with cortical blindness with 3 months of uncontrolled seizures post insult. Therefore, it is important for the

clinicians to note the frequency of seizures including the last episode for better understanding of the child's visual functioning.

7.7 Repeatability of visual functions with associative factors

It is well known that repeatability of visual functions decrease in individuals with vision impairment. However, in children with CVI, the differences in the test-retest measures are likely to be attributed to factors beyond their vision impairment, such as: seizures, medication, overall development, severity of brain damage as noted in brain imaging as stated in section 7.6.

In the current study, no specific factor could be identified to affect the repeatability indices of both VA and CS tests. However, it is important to acknowledge that we had small sample size (n=21 in children with CVI and n=16 in controls) which could have been a limiting factor for determining this.

Chapter 8 : General discussion and Conclusions

8.1 General discussion

The current study provides extensive insights into the demographic and clinical characteristics of children with CVI which is representative of the current situation in a developing country such as India. While several studies on children with CVI have investigated high-functioning groups of CVI (Chandna et al., 2021; Chokron et al., 2021; Pilling et al., 2022), this is the first study to primarily include a low and moderate functioning cohort (72.3%). The vision assessment in the latter group is much more challenging due to their limitations in several developmental milestones. Therefore, having validated visual function tools in this cohort is very important, which the study addresses with the currently existing (TAC-II and HH cards) and newer (the PV app and OCC) VA and CS tools. Neonatal hypoglycaemic brain injury was reported to be the most common cause of CVI in our cohort (47.6%), as opposed to HIE reported in other studies. This is reflective of the current situation that maybe region specific to emphasize on preventable causes such as neonatal hypoglycaemia with improved antenatal and postnatal care. Our study also provides an understanding of the parent-reported visual concerns in children with CVI and attempted to determine its association with vision-related parameters. Through parent-reported concerns we are able to provide important visual concerns that neurologists and other healthcare practitioners could include as part of their history taking protocol which can serve as an easy referral parameter. Only one-third of the parents/caregivers considered bringing their children for comprehensive eye evaluation, despite referral and phone-call reminders. However, a majority of the study cohort were outside city/state limits and therefore travelling was a major concern as reported by parents in addition to the restrictions imposed due to the pandemic.

In the current study, the primary aim was to validate the clinical tools that are used to measure visual functions in children with CVI and age-similar typically developing children. The TAC-II and HH cards were tested against the relatively newer PV app and OCC for acuity and CS testing respectively. We noted that the 95% LoA between the tests were wider in children with CVI (TAC-II vs. PV app: -1.03 to 0.53 logMAR and HH cards vs. OCC: -0.37 to 0.49 logCS) as compared to the chronologically age-similar controls (TAC-II vs. PV app: -0.72 to 0.44 logMAR and HH cards vs. OCC: 0.06 to 0.49 logCS). Literature suggests that the VA tests used in the paediatric population compare poorly to the tests used in the adult population (Anstice et al., 2017; Mody et al., 2012; Shah et al., 2012). This is primarily due to variability in responses from children when compared to adults. The optotypes that are commonly used for adults include letters (Kaiser, 2009) or tumbling E and Landolt C charts for those who are not familiar with letters (Treacy et al., 2015). All the optotypes have undergone thorough clinical validation and are available as standard logMAR charts (Caltrider et al., 2023). While these charts are used in children as well and are likely to reach adults levels of validity in older children, this may not be the case in young children. Therefore, based on the chronological age,

comprehension skills and the child's cooperation, the need to test using different visual stimuli arises (such as: gratings, pictures and symbols). In our current study, primary reasons for this significant difference between tests of VA could be attributed to differing step sizes and nature of tests (as in TAC-II and the PV app) and in tests of CS it could be different stimuli (picture as in HH cards vs. gratings as in OCC) and varying step sizes between the tests. In addition to the inherent variability that exists in the responses of even typically developing children, there could be group-specific reasons as well. In children with CVI, general and visual behaviour related concerns, such as recent seizure episode, change in the type and dosage of seizure medication, drowsiness (primarily due to seizure medication) (Jimenez-Gomez et al., 2022), temper tantrums, poor visual attention span and difficulty to adapt to visually novel targets (Chang et al., 2022) could also contribute to variability in the responses. However, when the tests have wide LoA, it is important to consider their repeatability indices in that specific cohort for clinical decision making.

An important part of the validation process is the repeatability indices of the test. TAC-II and OCC were noted to be the most repeatable in both groups, i.e., in children with CVI (CR (logMAR): TAC-II: 0.33 and PV app: 0.63; CR (logCS): HH cards: 0.36 and OCC: 0.11) in the controls (CR (logMAR): TAC-II: 0.27 and PV app: 0.41; CR (logCS): HH cards: 0.27 and OCC: 0.08). In the current study, a test-retest duration of within 2 weeks was considered in order to avoid any potential effect of visual development as much as possible. Teller acuity cards-II is one of the most popularly used grating acuity tests and has been tested extensively for its repeatability indices in several groups of young children (Hall et al., 2000; Johnson et al., 2009; Joo et al., 2020). Ohio contrast cards, however is a newer tool for measuring grating CS with a couple of studies finding good repeatability performance in school-going children with vision impairment (Hopkins et al., 2017; Osman et al., 2021). Ours is the first study to determine the clinical utility of these cards in one of the most challenging cohorts of children with SEN and there were found to have good repeatability indices in children with CVI and in typically developing children. Another important finding is that in the current study, we noted about 2 cards repeatability difference with TAC-II and within 1 card repeatability difference with OCC and we also note that functional vision was marginally strongly correlated with CS ($r=0.86$, $r^2=0.73$, $p<0.001$) when compared to VA ($r=-0.83$, $r^2=0.68$, $p<0.001$). These findings indicate that CS is a very important parameter to be captured in children with CVI.

The visual performance in children with CVI is likely to be influenced by several factors such as seizures and other developmental areas of the child. We found that children with a recent episode of seizure (i.e., within 3 months duration) as reported by parents/caregivers are more likely to have

significantly poorer VA, CS and functional vision score when compared to those for whom the last seizure episode was more than 3 months ago. With relation to the developmental age, an increase in developmental age was noted to explain the developmental trend in visual functions better than that of the chronological age in children with CVI. Therefore, while examining a child with CVI, it is important to plan the battery of tests based on the child's developmental age (if available), or understand the child's developmental delays through observation, interaction and asking parents/caregivers. This would enable the clinician to not limit the examination protocol to chronological age-appropriate testing, but customize it accordingly especially when testing children with SEN.

8.2 Strengths and limitations of the study

The current study is one of the largest to test VA and CS values in a cohort of children with CVI, particularly in low to moderate functioning group and to validate the new tests against existing ones in the field of paediatric eye care. Although only a small sample of children were available for determining the repeatability indices, yet this is the first study to attempt reporting the repeatability values in commercially available tests (TAC-II and HH cards) of VA and CS and in the newer tests (the PV app and OCC). The association of the functional vision score carried out using the CVI range instrument to the visual functions is also first reported in this study. Eliciting visual concerns from parents/caregivers of children with CVI presenting to a pediatric neurology clinic is crucial as the neurologists are usually the first point of contact for these children. Fourteen unique visual concerns were reported by parents of children with CVI in the current study. Difficulty in face recognition and maintaining eye contact were noted as the most common visual concerns in children with CVI in the lower and moderate functioning group. Missing objects in the lower/side field followed by difficulty in maintaining eye contact were most commonly reported among children in the high functioning range.

We acknowledge certain limitations in the current study. The diagnosis of CVI was based on the history and neuroimaging findings as the data collection was primarily carried out in the paediatric neurology clinic. There could be few cases which may have been under-diagnosed due to normal MRI findings, however, efforts were made to refer to geneticist wherever genetic causes of CVI were suspected.

The higher spatial frequencies in the PV app has a 0.3 logMAR jump (i.e. 0.12 to -0.18 logMAR), which could result in higher variability in the test-retest measures. This variability in acuity measures should be considered particularly for children with good visual acuity when using in the clinics.The

repeatability data was only available in a small sample of children with CVI. Given the heterogeneity that exists among children with CVI itself, it is difficult to generalize the repeatability indices for all children with CVI (low, moderate and high functioning) from this study. As the data collection was primarily carried out during the pandemic, the estimated number of children as per sample size calculation could not be achieved. There was also a significant drop in parents/caregivers bringing their children for retest and also for comprehensive eye evaluation as per recommendations. Clinical evaluation such as refraction, amplitude of accommodation, posterior segment evaluation and therefore could not be carried out on all the children. Visual concerns could not be elicited in a small proportion of children when VA and CS assessments were completed first as per parents' preference as they had to report back to the neurology clinic. Squint and nystagmus assessment were attempted after data collection on the same day, but it could not be carried out for all children due to the limited time owing to the neurology consultation which was the primary purpose for the hospital visit. The attempt to perform these tests in between neurology consultations and other diagnostic procedures resulted in inconsistency in maintaining the order of testing across all children. Simple torch light examination was carried out to grossly assess for squint (Hirschberg test) and nystagmus in between the neurology visits, whenever possible. Therefore, this could have resulted in latent cases remaining undiagnosed.

We could not include the inter-examiner repeatability component in the current study which is important as the results are likely to be influenced in this challenging cohort based on the experience of the examiner. This could not be incorporated in the current study as second examiner performing the tests on the same day (either the test or retest visit) was not feasible as this would translate to the child undergoing more tests on a given day, which could reduce the attention span, increase fatigue and influence the visual function values. Although the influence of the testing time on the visual functions measurements is unclear. It would have been ideal to retest VA and CS at the similar testing time as that of the baseline visit. Nevertheless, implementing this was difficult due to practical issues like appointment slot constraints, parents' inability to reach the hospital promptly, and the child's restlessness. This can be better planned in the future studies by separating the study recruitment from the clinical consultation visits. The major challenge of implementing the ideal protocol in the current study can be primarily attributed to the pandemic. However, the overarching goal of validating the clinical tools of VA and CS was accomplished. The repeatability indices, however, have been established with a small sample and future studies are warranted to determine the same.

8.3 Clinical implications and recommendations

Implications for the eye care professional and vision rehabilitation specialists

The current study has several important clinical implications. The wider LoA between the tests of VA and CS indicate that the tests should not be used interchangeably in the clinic in children with CVI and also in the typically developing children, as the values maybe test specific and should be interpreted accordingly. It is important to be aware that some tests will overestimate and be familiar with age-based norms for the test in use in the clinic. This helps in cases when a patient is referred from another clinic and a different test was used to estimate VA and CS values. Through this study, we understand that the PV app over-estimates VA by 0.25 logMAR and 0.14 logMAR in children with CVI and typically developing children respectively when compared to TAC-II. Similarly, OCC under-estimates CS by 0.06 logCS and 0.27 logCS in children with CVI and in age-similar controls respectively when compared to HH cards.

It is also important to interpret the change in the VA and CS values specific to the test based on its repeatability indices. For example, a CR of 0.32 logMAR for TAC-II in children with CVI indicates that it would be a true change in the VA with TAC-II only if there is an VA change of more/less than 0.32 logMAR in the next visit. This is important to understand the effect of any intervention or the pattern in vision development.

Considering the better repeatability indices as identified in the study, albeit with a small sample, TAC-II and OCC are recommended to be used to test the VA and CS respectively in children with CVI. It is important to follow the same testing protocols across visits particularly when any intervention such as visual rehabilitation therapies are being pursued. This is important given that the range of variability between the tests is high (tables 7.1 and 7.2).

Eye care personnel should mandatorily document seizure history, including the last seizure episode and medication used in every visit. We found that VA is significantly different based on the recent episode of seizure and therefore change in the visual functions should be studied carefully based on the recent seizure episode. The functional vision assessment is an important part of the assessment that can be even carried out by a non-eye care personnel (such as vision rehabilitation specialist) using simple material (such as in Bradford visual function box (Pilling et al., 2016)). This assessment is also handy in planning rehabilitative strategies especially in case of children who are unable to cooperate for a visual function assessment. We found that based on the functional vision score when children were categorised into 3 phases, the visual functions of the children were found to be significantly different

across the 3 phases of CVI. As CVI involves damage to the higher-order visual processing functions, tests as discussed in section 2.4, are essential in addition to the basic visual functions such as acuity and CS.

Implications for the paediatricians, developmental psychologists and paediatric neurologists

The association of developmental age with vision-related parameters such as VA, CS and functional vision implies that the paediatricians, developmental psychologists and neurologists could consider referring such children for comprehensive eye evaluation and vision rehabilitation. We also demonstrated that parent-reported visual concerns can also serve as a quick referral parameter, however it should also be kept in mind that parents may not be able to report a visual concern, even when the visual functions could be poor. Hence relying only on parent-report may not suffice. Early intervention therapists primarily physiotherapists, occupational therapists, speech therapists and special educators regularly interact with children having developmental delays with underlying causes of neurological conditions such as cerebral palsy as part of their therapy sessions. With approximately 60-70% of children with cerebral palsy also having CVI (Schenk-Rootlieb et al., 1994; Uggetti et al., 1996), it is important to raise awareness and educate the professionals about the vision challenges these children are likely to have.

8.4 Reflections

There are few important reflections through the current study. As the study cohort included children with CVI and typically developing children of very young age, it was difficult to accommodate all the battery of study tests on the same day, including the clinical consultations (for children with CVI). It is therefore suggestible to recruit the children on a separate day for the study purposes. However, this was primarily not possible in the current study due to the pandemic and also as there were no transport charges provided for the additional visit for study purposes. This resulted in only few children undergoing important assessments such as refraction and posterior segment examination. Inter-examiner repeatability, which is an important component of test validation could not be undertaken in this study. Inter-examiner repeatability is crucial particularly when assessing children with any causes of SEN, for e.g., CVI, as in this study. This is considering the variability in the cohort and the experience of the examiner, both of which are likely to influence the vision-related parameters of the child. Also, as there was no funding for getting the latest MRI brain testing done, in the current study we had to rely on the earlier films and could not draw strong conclusions from the findings. The choice of tests, such as using the recently developed Mayer-Kran Double Happy test (Mayer et al., 2020),

which has finer step sizes for CS assessment could be considered as step sizes do play an important role for comparison with another equivalent test and also within itself (repeatability). Quantifying visual fields would have helped us understand the parental concerns of bumping into objects better and missing objects placed on the lower field, which were reported in our study. Despite the above-stated concerns, the current study offers several important clinical take-aways for both eye-care professionals, vision rehabilitation specialists, paediatricians, paediatric neurologists, developmental paediatricians and developmental psychologists (as mentioned in earlier section 8.3).

8.5 Conclusions and scope for future research

As part of the validation process of the clinical tools used to measure VA and CS, we conclude that wider LoA was obtained for children with CVI as compared to the chronologically age-similar controls and therefore the tests (TAC-II and the PV app for VA and HH cards and OCC for CS) should not be used interchangeably in both groups of children (i.e., in CVI and in controls). Each test had different repeatability indices and TAC-II and OCC were found to have better repeatability indices in both the groups. It is important to report the test-retest values that are specific to the test being used to avoid misinterpretation of change in visual functions. When assessing children with CVI, eye care personnel should cover detailed birth and developmental history, seizure history, parent-reported vision concerns and other developmental milestones and any rehabilitation therapies availed to have a comprehensive understanding of the child's visual performance and for effective planning of rehabilitative strategies. The chief visual concerns, as discussed in the current study could be useful for non-eye care professionals to refer the children for comprehensive eye evaluation.

As there could be variability in CVI cohort itself based on the severity (Pehere & Jacob, 2019), future studies determining the repeatability indices based on the low, moderate and high functioning group with adequate sample size in each group will be useful. The tests of visual functions validated and noted to be repeatable in the current study (i.e., TAC-II and OCC) can be used to determine effectiveness of interventions (such as rehabilitative, medical, optical and surgical) carried out in children with CVI. It would also be interesting to note how these behavioural vision tests (such as VA, CS and visual fields) compared to more objective tests (such as VEP) and also using eye tracking paradigm in this challenging cohort.

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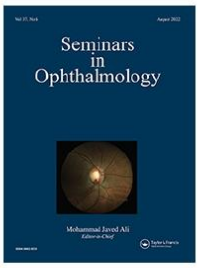
Appendix

A1. Seminars in Ophthalmology publication



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Grating acuity tests for infants, young children and individuals with disabilities: A review of recent advances

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REVIEW

Grating acuity tests for infants, young children and individuals with disabilities: A review of recent advances

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ABSTRACT

Background: Accurate measurement of visual acuity is important in managing any ocular condition. Measuring visual acuity has always remained a challenge in infants, young children and individuals with disabilities who are unable to respond verbally. A variety of pediatric acuity tests that include both grating and recognition acuities have been described in the literature, some of which are outdated. This review paper aims to summarize the currently available and recently developed grating acuity tests that can be used for infants, young children and individuals with disabilities.

Methods: A review of literature was carried out to identify tests that were currently available and recently developed. Additionally, search was also done on popular search engines and websites of companies. Tests identified were screened for availability and investigated for validity through published research in peer-reviewed journals.

Results: A total of eight grating acuity tests were identified, out of which six of them were paper-based tests. The remaining two tests were app-based tests with established data for the typically developing pediatric cohort. The repeatability indices were available only for four grating acuity tests.

Conclusions: This review paper summarizes the basic features of the grating acuity tests and importantly, the parameters that determine the clinical utility of the tests such as the testability, acuity range, specific cohort studied, testing time and reliability indices. The paper also discusses the recent technological advancements in the field of acuity testing for the pediatric cohort and its comparisons with the conventional methods when available.

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Grating acuity; Infant vision; Pediatric visual acuity; Vision in individuals with developmental delays and disabilities; Vision in pre- or non-verbal children

INTRODUCTION

Visual acuity remains as one of the most important parameters to determine the outcomes for managing various ocular conditions. Measuring visual acuity in those who cannot endure the regular reading of optotypes has always remained a challenge. Such a challenge is not necessarily restricted to the pediatric age group but can also include adults who have some disabilities that restricts them to give a coherent verbal response. This cohort mostly comprises of either pre- or non-verbal individuals. Pediatric visual acuity charts and tests are therefore designed to be able to quickly measure through behavioural observations by the examiner, negating the need of a verbal response from the tested individual. A variety of pediatric visual acuity tests exist and the choice of test to be used in the clinic usually depends on the chronological age of the child. However, age-appropriate tests may or may not always be helpful in measuring the acuity. Other factors that will determine the choice of the test includes familiarity (to task), cooperation and comprehension skills of the child. Few tests measure the grating acuity (using black and white striped patterns) and many tests measure recognition acuity (using optotypes such as symbols, pictures, numbers and letters). Studies have shown that acuity estimates obtained from grating and recognition acuity tests are not comparable,[1,2] this could primarily be attributed to the differences in the complexity of the tasks. Grating acuity, however, is used as an important marker to screen for ocular abnormalities,[3] to determine the effectiveness of an intervention (medical, optical or surgical) and in long-term clinical follow-up of non-verbal individuals.

Grating acuity uses preferential looking paradigm and can be used in infants, young children and in individuals with disabilities who are unable to respond to the recognition acuity tests. An inherent assumption in these tests is that the individual would instinctively prefer to look at a pattern rather than a homogenous background of equal luminance.[4] The clinician administering the test will have to make a decision on the direction in which the patient is looking, usually under a 2-alternate forced-choice paradigm, without knowing the actual location of the grating. Performing this test is considered as a double psychophysical procedure, with both the infant and the examiner as being subjects in it.[5] The chances of guessing a "correct" look in a 2-alternate forced choice is 50%. With recent app-based tests four or more alternate forced-choice test[6] can also be performed, increasing the measurement precision (only 25% chances to guess right in 4-alternate forced choice).

The clinical utility of an acuity test can be measured by testability, testing duration, ease of administering the test, engagement ratio, the range of acuity that can be assessed

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Table 1. Summary of the basic specifications of currently available grating acuity tests.

Test name	Number of gratings	Spatial frequency range	Recommended test distances
Teller acuity cards-II	15 + 1 blank card	0.23 to 38.0 CPCM	9.5, 19, 38, 55 and 84 cms
LEA gratings preferential looking test	6 + 1 blank card	0.25 to 8.0 CPCM	28, 43, 57, 85 and 115 cms
Newborn acuity cards[#]	9 + 1 blank card	0.062 to 1.515 CPD	38, 55 and 84 cms
Keeler acuity cards	8 infant assessment cards 10 children's additional set	Infant assessment cards: 0.18 to 12.5 CPD Children's set:0.3 to 35.4 CPD	38 cms*
City-Cardiff preferential looking acuity test	17 + 1 blank card	0.3 to 38 CPD	50 cms
Patti stripes	6 + 1 blank card	0.3 to 9.6 CPCM	25, 50, 100 cms
Peekaboo Vision application	18 spatial frequencies can be tested at any given distance in the range of 25–50 cms	2.21 to –0.18 logMAR	25 to 50 cms
Automated visual acuity test	9	0.29 to 14.5 CPD	64–66 cms

(CPD = cycles per degree, CPCM = cycles per minute, MAR = minimum angle of resolution)
*One study reports using longer working distances of 55 and 84 cms also[7]
[#]These cards will be available soon commercially (personal communication with the developer)

and repeatability indices. Several studies have used grating acuity tests in both typically developing young children and in the pre- or non-verbal cohort as a part of screening and/or interventional studies. An earlier review[8] published about a quarter century back summarized several studies in which acuity card procedure has been used in both typically developing young children and in those with various causes of additional disabilities. However, several of these acuity cards are currently not available for clinical use. Hence, there is a need to review and update the currently available grating acuity tests along with electronic tests that are getting developed in recent times that can be used in infants, young children and individuals with disabilities.

METHODS

A literature review was undertaken to identify the appropriate tests. This was done by using keywords such as grating acuity, pediatric visual acuity, infant vision, vision in pre- or non-verbal children and vision in individuals with developmental delays and disabilities in PubMed, Google Scholar search engines. Additionally search was also undertaken in the popularly known commercial websites that manufacture ophthalmic instruments and tools like Precision vision, Good-lite, Stereo Optical etc. The search strategy followed was intended to identify all the currently available grating acuity tests and also the recently developed app-based tests with established normative data. Table 1 summarizes the basic specifications of the currently available grating acuity tests. This review also focuses on the various parameters that determine the clinical utility of these tests along with their expected normative values (Table 2).

Teller Acuity Cards-II

Teller acuity cards (TAC) are the most commonly used 2-alternate forced choice preferential looking tests in infants and pre- or non-verbal children[9] and also to test those with delayed developmental milestones.[10] These cards developed by Prof. Davida Teller, have been a time-tested measure with a good predictive validity of grating acuity in the pediatric population.[11] This predictive validity however was higher (73%–95%) only for those infants who had good visual acuity with TAC and not for those who had below normal visual acuity with TAC (predictive value 39%–80%). In this study, the infants were tested with TAC during infancy and with HOTV and TAC at 48 months of age.[11]

A modified version of these cards, called as Teller acuity cards-II have been produced by the Stereo Optical Company, Chicago, as the original cards were no longer being produced by Vistech Consultants, Inc., Dayton, OH.[12] The two important differences between the two versions is the lamination of the cards and minimizing the visibility of the grating edge by finishing with half of the black or white stripe of that respective grating card[13] in the modified version, which can help minimize the chances of detection using the edge artifact.[14]

The age-based normative monocular and binocular acuities have been studied previously using the original TAC.[15] However, in comparing the age-norms based on the original TAC with the modified and commercially available TAC-II it was noted that the acuity values obtained using the former cards needs to be adjusted to approximately 0.5 octave[1] towards the lower acuity to be comparable to TAC-II (for e.g. 19 cycles per degree (CPD) obtained with original TAC can be adjusted to 13 CPD in TAC-II).[12] The TAC-II (Stereo optical) includes 17 cards (25.5x55.5 cms) with a 4 mm peephole in the centre of the card for the examiner to view the child's response. Square-wave gratings are present on one side of the card with a grey background (with approximately 35% reflectance) on the other half. The range of spatial frequencies include: 0.23 (low vision card), 0.32, 0.43, 0.64, 0.86, 1.3, 1.6, 2.4, 3.2, 4.8, 6.5, 9.8, 13.0, 19.0, 26.0, and 38.0 cycles per centimeter (CPCM) and a blank card. The recommended test distances include 38 cm, 55 cm and 84 cm. Cycles per centimeter approximately equals CPD at 55 cms[13] (exact at 57.2 cms, when considering a circular shaped card.[16]) However, for other testing distances

[1]Octave is doubling or halving of spatial frequency.

Table 2. Clinical utility indices of available grating acuity tests collated from different studies.

Test name	Study	Cohort	Age range	Acuity ranges obtained	Testability rate (%)	Testing time	Repeatability	Remarks
Teller acuity cards-II*	Clifford et al[12]	Infants and children with no ocular problems (n=60) 3.5-month-old, n=20 11-month-old, n=20 30-month-old, n=20	3.5-30 months	Overall, across all the ages: 0.47 octave better with TAC as compared to TAC-II At 3.5 months: 0.2 octave At 11 months:0.4 octave At 30 months: 0.7 octave	87%	-	-	Acuity estimates obtained by TAC-II are lower as compared to TAC and need to be adjusted by approximately 0.5 octave
	Johnson et al[17]	Children with multiple sensory, visual, auditory, motor and/or cognitive impairments (n=21)	5-21 years	Mean=-0.09 to 1.85 logMAR (median:0.1 logMAR, mean: 0.82 ±0.47 logMAR)	95%	204 ± 111 s	±0.60 logMAR	Comparable acuity estimates with Cardiff acuity cards. Higher variability noted with Cardiff acuity cards
	Qiu et al[18]	Normal infants (n=244)	5-24 months	Mean acuity across all age ranges: B/O: 0.17 to 0.83 decimal; M/O:0.15 to 0.8 decimal	B/O:98.7% M/O:89.2%	Tests completed within 2 to 5 min	-	All children reached adult-like acuity of 26 CPD at 24 months of age
	Leone et al[19]	Typically developing children (n=1404, total; TAC-II on n=544, B/O; n=442, M/O)	6 to <42 months	Mean acuity ranges (95% prediction limits) : from 6 to <9 months: B/O: 6.33 (3.57–11.20) CPD; SD: 0.41 octave to ≥33 months: 12.60 (5.53–28.73) CPD; SD:0.58 octave from 6 to <9 months: B/O: 5.72 (2.78-11.76) CPD; SD: 0.52 octave to ≥33 months: 11.81 (5.04–27.7) CPD; SD:0.59 octave	B/O: 94% M/O: 76%	-	-	Significant improvement in acuity estimates were noted with age: r^2:0.29, p<0.0001, B/O; r^2:0.32, p<0.0001, M/O
	van der Zee et al[20]	Typically developing school children (n=60) Children with ocular abnormalities (n=21) Children with suspected brain damage (n=26)	3-12 years	Median Snellen equivalent Typically developing: 20/11.6 Ocular abnormalities: 20/17.5 Suspected brain damage: 20/11.6	Typically developing:98.3%; Ocular abnormalities:71.4%; Suspected brain damage:92.3%	-	-	Crowding ratio was noted to be a better indicator than visual acuity to detect children at risk of cerebral visual impairment
	Xiang et al[21]	Normal infants and toddlers (n=218)	Birth-36 months	Mean acuity ranges (lower to upper limit) from 2-3 months: B/O: 1.18 (0.41 to 3.42) CPD to 34-36 months: 12.01 (3.1 to 46.5) CPD; from 2-6 months: M/O: 1.97 (0.55 to 7.06) CPD to 34-36 months: 10.75 (4.75 to 24.34) CPD	B/O: 98.6% M/O: 50.2%	-	-	Normative visual acuity norms for infants and toddlers from southern China
LEA gratings preferential looking test	Martini et al[22]	Normal infants (n=133)	<4 months	At 1 month: 0.55 ±0.70 CPD At 2 months: 1.35 ±0.69 CPD At 3 months: 3.11 ±0.54 CPD	-	-	-	Acuities measured across 3-month to follow-up. Significant differences in acuities across the 3 months

(*Continued*)

Table 2. (Continued).

Test name	Study	Cohort	Age range	Acuity ranges obtained	Testability rate (%)	Testing time	Repeatability	Remarks
	Deshmukh et al[23]#	Preverbal (<3 years) and older nonverbal children (with developmental delay) (n=31)	4-44 months	Mean B/O acuity: 2.07CPD±1.34 octave; Mean M/O acuity (RE): 0.98 CPD ±1.96 octave; Mean M/O acuity (LE): 0. 89 CPD ±1.61 octave	B/O: 100% M/O: 72%	-	Inter-observer agreement (for B/O and M/O): within 0.5 octave for 94.2% observations	-
	Mody et al[24]	Normal children (n=200) Unilateral strabismic or anisometropic amblyopic group (n=30)	6 months-3 years	B/O: 1.0 ± 0.6 logMAR (range: 0.5 - 2.1) M/O: 1.15 ± 0.15 logMAR (range: 0.88 - 1.48)	-	B/O:26.5 ± 5.0 s (range: 20 - 50) M/O: 23.1 ± 4.6 s (range: 20 - 50)	-	Better acuity estimates were noted with Cardiff acuity cards as compared to LEA gratings
	Yudovich et al[25]	Infants and toddlers (including 2 with preterm births)	5 weeks to 17 months	Mean B/O acuity at 0–4 months:3.8 CPD; 12-16 months of age:10.2 CPD Mean M/O acuity at 0–4 months:2.7 CPD; 12-16 months of age:10.4 CPD	-	-	-	TAC and LEA gratings preferential looking test had strong correlation (r=0.993, B/O; r= 0.991, M/0). Intrasubject correlation was noted with TAC and LEA gratings preferential looking test were: r=0.505, B/O; r=0.615, M/O
Newborn acuity cards	Brown et al[26]	Healthy newborn infants (experiment 1, n=47; experiment 2, n=22)	Newborn infants (median birth age: 1 day, 95%:<2 days)	Range: B/O: 0.783 to 1.204 CPD	-	-	-	Psychophysical methods were primarily tested: method of constant stimuli and descending method of limits
Keeler acuity cards	Livingstone et al[6]	Typically developing children with and without visual problems (n=58, study 1; n=60, study 2)	2-60 months	Median acuities: Study 1: 0.4 logMAR (range: 0.1 to 1.6 logMAR) Study 2: 0.3 logMAR (range: 0.1 to 0.9 logMAR)	Study 1: 90.8% Study 2: 95.5%	B/O: 251 s	Study 1: 95% LoA of -0.427 to 0.323 logMAR (CR=0.37) Study 2: 95% LoA of -0.432 to 0.407 logMAR (CR=0.42)	Study 1&2: Repeatability was found to be similar for binocular and monocular viewing conditions
	Neu & Sirteanu [7]	Typically developing children (n=95)	7-78 months	Mean acuities (CPD) M/O: 19-35 m:14.5±4.4 36-47 m: 25±7.2 48-59 m: 26.2±8.3 60-71 m: 29.1±8.4 72-78 m:31.4±11.9	98.9%	-	-	Was found to have comparable age norms as measured with TAC
	Mackie et al[27]	Children with neurological impairment (n=91)	8-19 months	0.00 to 2.2 logMAR	91%	-	-	Was compared with Cardiff acuity cards
Peekaboo Vision application	Livingstone et al[6]	Typically developing children with and without visual problems (n=58, study 1; n=60, study 2)	2-60 months	Median acuities (for all children): Study 1: 0.5 logMAR (range: 0.1 to 1.9 logMAR) Study 2: 0.2 logMAR (range:-0.18 to 0.9 logMAR)	Study 1: 93.6% Study 2: 94.9%	B/O:185 s	Study 1: 95% LoA of -0.283 to 0.198 logMAR (CR=0.27); Study 2: 95% LoA of -0.413 to 0.437 logMAR (CR=0.32)	Study 1: Repeatability was found to be slightly poorer for binocular viewing condition compared to monocular Study 2: Similar repeatability indices noted for both viewing conditions

(*Continued*)

Table 2. (Continued).

Test name	Study	Cohort	Age range	Acuity ranges obtained	Testability rate (%)	Testing time	Repeatability	Remarks
Automated visual acuity test (AVAT)	Vrabic et al[28]	Healthy children (n=36)	5 months-16 years	-	97%	Was set for 3 min + 24 s	-	Acuity overestimation with AVAT was observed for >0.4 logMAR on standard tests and underestimation on AVAT for ≤0.4 logMAR on standard tests. Less sample in <3 years group (n=4). Standard tests included in the study: Keeler acuity cards and LEA symbols.

B/O = binocular, M/O = monocular, s = seconds, min = minutes, MAR = minimum angle of resolution, CPD = cycles per degree)
*The search results of Teller acuity cards-II have been given
#The acuity estimates of only observer 1 have been given

(≥ 20 cms), the appropriate conversion formula should be used (Equation 1). In case of using closer testing distances, this formula should be avoided considering the relatively larger distance between the grating patch and the central peephole.[13]

$$\text{CPD} = (\text{Testing distance}/55)\text{XCPCM}(\text{at 55 cms, CPCM} = \text{CPD}) \quad (1)$$

For e.g. 10 CPCM at 38 cms = (38/55) X 10 = 6.9 CPD

CPD = cycles per degree, CPCM = cycles per centimeter

The TAC comes with a testing stage that is useful for mounting the cards and eliminating peripheral distracters while the testing procedure is in progress (Figure 1a).[13] The visual acuity measures were found to be comparable with and without the stage for age groups 3.5, 11 and 30 months, and not for the 17 months old age, where the acuity was poor without the stage.[29] Comparison of the inter observer agreement of acuities obtained using TAC in children with ocular or neurological disorders, or in combination with healthy preterm children revealed that the inter-observer agreement was within 1 octave or better in both the groups in 96% of the binocular test–retest comparisons. However children with ocular or neurological conditions may take additional testing time (clinical group, average time taken = 3.6 ± 1.9 minutes; control group, average time taken = 2.4 ± 0.6 minutes).[30] Teller acuity cards has also been used previously for measuring acuity in children within the age range of 3–109 months with cerebral palsy with a good success rate (88%).[31]

LEA Gratings: A Preferential Looking Test

LEA gratings (Good-lite company[32]) is another commonly used preferential looking grating acuity test in children. The grating paddle developed by Prof. Lea Hyvarinen, has age normative data.[33] The LEA gratings paddle does not use a testing stage and hence is more portable. It consists of 4 paddles with 6 gratings and a solid grey background paddle (Figure 1b). Each paddle is of 20 cm diameter. The acuity range that can be measured using LEA gratings preferential looking test include: 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 CPCM. The commonly used test distances are 29 cm, 57 cm and 86 cm.[16] Care should be taken to move both the blank and the grating paddle equally, when observing the individual's eye movement. This test should be differentiated from LEA gratings discrimination/resolving test.[34]

The acuity estimates measured with LEA gratings and TAC have been noted to have a close correlation (r = 0.993, binocularly; r = 0.991, monocularly) in infants from 5 weeks to 17 months of age.[25] LEA gratings have also been successfully used in children with Down syndrome, hearing impairment and other cognitive impairments from 3 to 18 years of age.[35]

Newborn Acuity Cards

Newborn Acuity Cards were developed by Prof. Angela Brown.[26] These cards vary from TAC in that the square wave gratings (24.8 cms) consisting of black and white stripes are placed in the centre of the card (Figure 1c). The gratings are placed in the centre to avoid mis-estimating the acuity in infants and children who may have peripheral or right/left field defect. The overall dimensions of the card are 30.5 × 61 cms.[36] These cards were found to be successful in measuring grating acuity in normal, preterm newborn and full-term newborn infants with no ophthalmologic abnormalities. The cards were noted to have 89% success rate for testability and were simple, reliable and fast.[26] The clinical utility of these cards in children with developmental delays is yet to be determined.

Keeler Acuity Cards

Keeler acuity cards measure the grating acuity and follows the 2-alternate forced choice preferential looking paradigm and are clinically used predominantly in the European countries.[37] Monocular acuities in children aged 1–6 years were found to be comparable between Teller acuity and the Keeler acuity cards (children's additional set).[7] However, the spatial frequencies of both sets of cards are not identical.[7] Keeler acuity cards are available in 2 sets, namely the 'Infant assessment set' and 'Children's additional set'. Both the sets have cards with the following dimensions: 26.5 × 57.5 cms made of plastic composite for durability. Each card contains 2 circles with a diameter of 10.3 cms and having a white border of 1 mm thickness. One of the circles has the gratings while the other circle has homogenous grey background as the card (Figure 1d). The examiner views the child's response through the central peephole.

The infant assessment set consists of 7 cards plus one blank card. Acuities in the range of 0.18 to 12.5 cycles per degree can be measured at 38 cms testing distance. For children beyond 1 year of age, the children's additional set is used. This set includes 10 cards in the range of 0.3 to 35.4 CPD when tested at 38 cms.

City-Cardiff Preferential Looking Acuity Test

The City-Cardiff preferential looking acuity test also presents gratings enclosed in a circle similar to the Keeler acuity cards (Figure 1e). The cards have been developed by a team of clinical vision scientists from City, University of London and Cardiff University, United Kingdom. The cards are available in a flip format, hence is easily portable. The cards can be placed on the 'A' shaped display stand that avoids the distraction of the examiner holding the cards. There are 17 cards (2 cards per spatial frequency) that range from 2.0 logMAR (0.3 cycles per degree) to −0.1 logMAR (38 cycles per degree). The dimensions of the cards are: 22.2 × 30.2 cms, circle diameter: 7.45 cms). The recommended testing distance is 50 cms.[38] The grating acuity notations are provided in logMAR, Snellen fraction and cycles per degree. The clinical utility of these cards is yet to be established as no studies have reported the use of these cards till date.

Patti Stripes

Patti stripes consists of six square-wave gratings that range from 0.3 to 9.6 CPCM. The gratings are printed on either side of the three paddles and one more paddle consisting of solid grey (blank) background that are square shaped

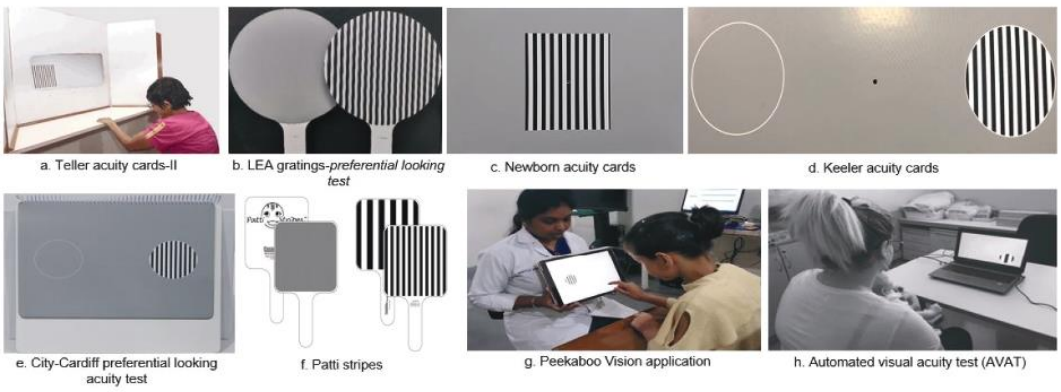

Figure 1. Grating acuity tests identified through literature search. *(Informed consents obtained from parents for figures 1a and 1 g; figures 1 f and 1 h reprinted with permission).*

(dimensions: 17.8 × 32 cms) (Figure 1f). The three recommended test distances are 25, 50 and 100 cms. The paddles are made of plastic (4 mm) and are very durable.[39] Similar to LEA gratings, equal movement of both the paddles (blank and the grating) should be made during testing. The clinical utility of these cards is yet to be established as no studies have reported the use of these cards till date.

Peekaboo Vision Application

Peekaboo vision (Figure 1g) is a digital-tablet-based interactive application that has been developed to be used on iOS platform to measure the grating acuity in children.[6] The tool's reliability indices were found to be comparable in two different settings to the Keeler acuity cards. (study 1-Malawi; the mean acuity difference between Peekaboo Vision and Keeler acuity = 0.02 logMAR, 95% limits of agreement = 0.33 to 0.37 logMAR; study 2-United Kingdom; the mean acuity difference between Peekaboo Vision and Keeler acuity = 0.01 logMAR, 95% limits of agreement = −0.413 to 0.437 logMAR).[6] While the earlier study was carried out using an earlier prototype of the application, the second study used the updated build. On test–retest measures, better repeatability was noted with Peekaboo Vision app compared to Keeler acuity cards in both the studies (study 1, 95% LoA: −0.283 to 0.198 logMAR with coefficient of repeatability (CR) of 0.27; study 2, 95% LoA: −0.344 to 0.320 logMAR with CR of 0.32. Better child engagement was noted with Peekaboo Vision application in the first study.[6] The clinical utility and reliability indices of the Peekaboo Vision application in children with special needs is yet to be established.

Automated Visual Acuity Test (AVAT)

The development of AVAT was recently published.[28] This automated testing requires a minimum skilled examiner and was found to be testable even in children as young as 5 months of age. The testing equipment consisted of an eye tracker (remote eye tracker Tobii Pro X3-120 (Tobii AB, Stockholm, Sweden) that was set below 15.6-inch LCD screen (laptop HP Zbook G5). Sampling rate of 120 Hz was used to record the binocular gaze data. A 5-point binocular calibration was used. Nine grating acuities ranging from 2.0 to 0.3 logMAR were presented on the computer screen in a 2-alternate forced-choice paradigm. There are six different layouts of the circle across the screen (Figure 1h). The testing distance was set at 64–66 cms. Two circles of diameter 70 mm (with 1 mm border thickness) were placed on the grey background (330 × 185 mm) for the presentation. The distance between the centers of the 2 circles was maintained at 112 mm and the placement of the circles were set at 11 mm from the upper and lower background borders and 37 mm away from lateral.[28]

The agreement between the acuity estimates obtained with AVAT and conventional tests like Keeler acuity cards for the preverbal group and LEA symbols for the verbal cohort was found to be fair with the Lin's concordance coefficient of 0.53 (95% confidence intervals: 0.31 to 0.72). However, an overestimation of acuity with AVAT was noted for children who had >0.4 logMAR using the conventional tests and underestimation for those whose acuity was ≤0.4 logMAR.[28]

SUMMARY AND CONCLUSIONS

This paper summarizes the currently available grating acuity tests used to test infants, young children and individuals with disabilities. The testability rates of the grating acuity tests combined for monocular and binocular testing ranged from 50.2% to 100% across all the tests among different cohorts of patients that includes typically developing children and children with other disabilities (visual and/or additional disabilities). LEA gratings preferential looking test showed the shortest testing time (20–50 seconds) for both typically developing children and those with visual impairment. Only four of the eight available tests have established repeatability indices with 95% LoA ranging from −0.6 to 0.6 logMAR across different cohorts of patients. Teller acuity cards-II has been most used in many published research when compared to all other grating acuity tests (Table 2).

Clinicians often rely on the grating acuity measurements, to manage young children, to study the effectiveness of a particular intervention and treatment outcome. This comprehensive

review can help the clinician to know and chose from the varied available grating acuity tests and apps based on what will be suitable for their patient cohort. With increasing use of electronic gadgets, and apps being developed, and with the wear and tear of apps being lesser when compared to card or paper-based tests there could be a greater shift towards using these tools, and hence it will be important to study apps utility as well. On the flip side, apps need to be constantly updated and could go outdated if the support and maintenance is not in place.

The reliability indices as discussed (Table 2) vary from test to test and it is important to consider the established norms to interpret the outcomes appropriately. Although, few studies report comparable acuity estimates between few of these tests,[7,25] one should be careful not to use these tests interchangeably, as acuity estimates may not be the same with different tests.[24,28] It is important to mention the test that is used along with the acuity measured in clinical documentation. Testing distance should be measured and documented appropriately as well to avoid over- or underestimation of the grating acuity. In case of using any non-standardized testing distances, it is important to incorporate the same into the formula (equation 1) to obtain the correct acuity measure.

The conventional card-based tests have been extensively used over the years by clinicians and researchers and few of them have well-established clinical utility indices.[24,35] However, with the technological advancements, there could be a need to digitalize the clinical tests given the advantages of portability, easier maintenance, child engagement etc. The two digitalized grating acuity tests discussed in this review are examples for this.[6,28] The proof of concept for digitalized testing of grating acuity in infants and children has also been demonstrated in other tests such as Dobson card[40] and adaptive computerized test of infant vision using eye tracking (ACTIVE).[41] More clinical validation of such digitalized tests in infants and young children is needed prior to its use in the regular clinical practice.

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A2. Scientific poster presented at the British Congress of Optometry and Vision Sciences 2020 conference

Parents reported visual concerns in a population of children with special needs in India

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INTRODUCTION

- Children with special needs have complex visual challenges compared to their typically developing counterparts[1-3]
- Identifying common functional visual difficulties in this group can help tailor clinical protocols to reduce examination duration
- This is particularly relevant during COVID-19 and also given the limited attention span in children

OBJECTIVES

This study aims to:

- Determine the common reasons that prompted parents/caregivers to bring their child(ren) to consult at a tertiary eyecare unit in India
- Associate commonly reported reasons for clinical attendance with visual functions

METHODS

- Retrospective review of medical records of children attending the Special Needs Vision Clinic for the first time at a tertiary eyecare unit in India during the months of April-May 2019
- Main purpose of the visit, clinical and demographic details of the children were recorded

RESULTS

- Fifty-one medical records of children consulting first time at the Special Needs Vision Clinic were reviewed *(Table 1)*

Characteristic	Results
Age (months) Mean±SD	120.7±73.2
Gender (n (%))	
Males	31 (61)
Females	20 (39)

Table 1: Demographic details of children attending the Special Needs Vision Clinic (n=51)

- The ocular diagnoses and the causes of special needs are mentioned in Table 2

Diagnoses	n (%)
Ocular	
Optic atrophy	16 (31.3)
Cerebral visual impairment	9 (17.6)
Refractive errors	9 (17.6)
Retinal pathologies	8 (15.6)
Strabismus	6 (11.7)
Lenticular abnormalities	3 (5.8)
Special needs	
Developmental delay	34 (66.6)
Down syndrome	5 (9.8)
Attention deficit hyperactive disorder	3 (5.8)
Cerebral palsy	2 (3.9)
Others (learning disability, Laurence-Moon-Bardet-Biedl syndrome)	7 (13.7)

Table 2: Ocular diagnoses and causes of special needs in children attending the Special Needs Vision Clinic (primary ocular diagnoses have been mentioned)

- The reasons for visit to the Special Needs Vision Clinic are captured in Figure 1

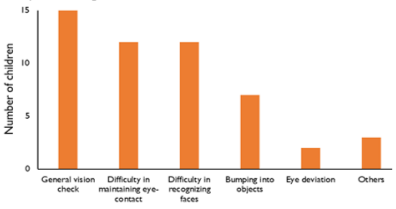

Figure 1: Reasons for attending the Special Needs Vision Clinic (others include copying from board, eye shaking)

- The associated visual functions for these most commonly reported reasons to visit are given in Table 3

Reasons	Associated visual functions/tests
Difficulty in maintaining eye-contact	Refractive error assessment Contrast sensitivity Binocular vision status Visual acuity Visual fields
Difficulty in recognizing faces	Visual acuity Contrast sensitivity Refractive error assessment Binocular vision status
Bumping into objects	Visual fields Contrast sensitivity Binocular vision status
Eye deviation	Binocular vision status Refractive error assessment Visual acuity

Table 3: Most commonly reported reasons and their associated visual functions/tests

CONCLUSIONS

- This study determined the most common reasons that prompted the parents/caregivers to bring their child(ren) to a tertiary eye care unit
- Based on the chief concerns, the order of testing can be modified instead of following a standard eye examination routine

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A3. British and Irish Orthoptic Journal publication

BIOJ
British and Irish Orthoptic Journal

Clinical Utility of 'Peekaboo Vision' Application for Measuring Grating Acuity in Children with Down Syndrome

ORIGINAL ARTICLE

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ABSTRACT

Peekaboo Vision is an iPad grating acuity app built with typically developing children in mind. Given the ease of using this app in the pediatric age group, this study determined its clinical utility in children with Down syndrome. Two groups of participants (children with Down syndrome and age-matched controls) were included. Presenting binocular grating acuity was measured using Peekaboo Vision and Teller acuity cards II in random order. Parents' feedback about their child's engagement and time taken to complete each test was documented. Thirty-seven children with Down syndrome (males = 23; mean age = 8.1 ± 4.2 years) and 28 controls (males = 15; mean age = 8.71 ± 3.84 years) participated. Time taken to complete the tests was comparable ($p = 0.83$) in children with Down syndrome. Controls were significantly faster with Peekaboo Vision ($p = 0.01$). Mean logMAR acuities obtained with Peekaboo Vision (0.16 ± 0.34) and Teller acuity cards II (0.63 ± 0.34) were significantly different ($p < 0.001$) in children with Down syndrome (mean difference in acuities: −0.44 ± 0.38 logMAR (95% LoA: −1.18 to 0.3). For controls, the mean logMAR acuity with Peekaboo Vision (−0.13 ± 0.12) and Teller acuity cards II (0.12 ± 0.09) was also found to be significantly different ($p < 0.001$) (mean difference in acuities: −0.24 ± 0.14 logMAR (95% LoA: −0.51 to 0.03) Peekaboo Vision test can be used on children with Down syndrome. Peekaboo Vision and Teller acuity cards II can be used independently but not interchangeably. The differences in the acuity values between the two tests could be a result of the differences in the thresholding paradigms, different testing mediums and the range of acuities covered.

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KEYWORDS:
Down syndrome; Grating acuity; Peekaboo Vision; Teller acuity cards II

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INTRODUCTION

Visual acuity measurements are a useful way of screening children for refractive error and amblyopia and can also be used to quantify the effectiveness of an intervention, setting rehabilitation goals and determining eligibility/level of impairment to avail supportive benefits (National research council, 2002; Anstice and Thompson, 2014). There are a number of tests that can be used to measure visual acuity in infants and children depending on their age and cognitive ability. These tests either make use of gratings or familiar objects such as an apple/house or even letters (Verweyen, 2004). Nearly all visual acuity tests have been developed for testing typically developing children (Anstice and Thompson, 2014). Although none of the tests have been specifically developed for children with additional disabilities, tests such as the Teller acuity cards (Good, 2001), Keeler acuity cards (Clarke et al., 1997) and LEA grating paddles (Pehere and Jacob, 2019) have been adapted for testing these children, as children with poor cognitive functions are thought to respond better to grating acuity and preferential looking paradigms (Pehere and Jacob, 2019). Clinical utility can be defined in terms of testability, testing time, comparison with other testing tools, range of acuity that can be measured and ease of using the tool.

Most children with special educational needs require assessment of visual functions to understand their visual capabilities, monitor treatment effectiveness and to provide feedback to parents. Therefore, it is essential to have suitable tests for this population as well. While various acuity charts including Cardiff cards and English alphabets are used for testing visual acuity in children with Down syndrome (Zahidi et al., 2018) not all children are familiar with these optotypes and language complexity may pose a challenge in carrying out these tests, particularly when English is not their native language.

Given the advancements in digital technology, there are an increasing number of vision tests being developed and used on electronic gadgets such as computers (Ehrmann et al., 2009; Laidlaw et al., 2008), tablets (Jones et al., 2019; Jones et al., 2020; Rodriguez-Vallejo et al., 2015; Malone et al., 2014) and mobile phones (Bastawrous, 2016; Brady et al. 2015). These tests have several advantages that could potentially make them attractive for children with special educational needs, such as audio/visual feedback (Livingstone et al., 2019), accessibility and familiarity (Kabali et al., 2015). The tests can also be carried out at home or in the community, as portability is no longer an issue, thereby allowing greater versatility (Tahir et al., 2014). Test stimuli can be randomized, preventing patients from memorizing responses (Jackson and Bailey, 2004). Many digital tests are available as freeware or at a low cost, which is an added advantage compared to conventional tests which can often be expensive (Ehrmann et al., 2009).

Several digitally available tests have been found to be useful in typically developing children with and without visual impairment (Rono et al., 2018; Laidlaw et al., 2003; de Venecia et al., 2018). One such test is the Peekaboo Vision application (version 1.5) (Livingstone et al., 2019), which could potentially lend itself well to testing grating acuity in children with special educational needs, including Down syndrome. It is a freely available digital tablet-based interactive application that has been developed on an iOS platform to measure grating acuity in children. The app provides video feedback of a happy cartoon face with a 'yippee' sound that helps maintain attention (Livingstone et al., 2019). The app has 3 different displays of 2 (0–12 months), 4 (12–24 months) and 9 (2 years+) target presentation that can be selected based on the age of the child. Acuities obtained using the Peekaboo Vision application were found to be comparable to Keeler acuity cards in typically developing children (study 1, mean difference: 0.02 logMAR (95% LoA: 0.33 to 0.37); study 2, mean difference: 0.01 logMAR (95% LoA: −0.413 to 0.437) and the application also had a higher engagement score (study 1: $p = 0.0005$) (Livingstone et al., 2019). The clinical utility of Peekaboo Vision in children with special educational needs is not yet known. Given the advantages, we hypothesized that Peekaboo Vision would have good clinical utility for children with special educational needs. The main aim of this study was to determine the clinical utility of the Peekaboo Vision application in children with Down syndrome and to compare it with the commonly used Teller acuity cards (Mash and Dobson, 1998), which was noted to have comparable acuity measures as the Keeler acuity cards in typically developing children below 6 years of age (Neu and Sireteanu, 1997).

METHODS

A prospective, cross-sectional study was carried out as a part of a comprehensive health screening program organized by a non-governmental organization for children with Down syndrome in March 2019. As a part of this program, vision screening was carried out by a team of optometrists and ophthalmologists experienced in managing children with special needs. The study protocol was approved by the Institutional Review Board of L V Prasad Eye Institute (LEC: 01-19-205). The study followed the tenets of the Declaration of Helsinki. Informed written consent was obtained from parents before enrolling participants into the study.

PARTICIPANTS

Parents of children less than or equal to 17 years of age with a confirmed diagnosis of Down syndrome were approached to participate in the study prior to the start of the screening process. All the parents expressed a willingness to allow their children to participate.

The authors acknowledge that the normal practice for children over the age of 3 years would be to use optotypes to measure visual acuity. We are aware that VA in children with Down syndrome can be successfully measured using a variety of charts, including Teller acuity cards, Cardiff acuity test, Keeler crowded, Kay pictures crowded and single optotype acuity tests (Zahidi et al., 2018). However, the clinical experience in India has been that a majority of children or adults having Down syndrome do not respond well to optotypes. This is largely a result of unfamiliarity with these optotypes. Therefore, all participants were uniformly measured with grating acuity. This also allowed us to compare the Peekaboo Vision application with Teller acuity cards II directly. Chronologically similar aged controls with no obvious ocular conditions were also included. Control participants were recruited from a residential complex and Sunday school.

CLINICAL TOOLS

Peekaboo Vision application

Peekaboo Vision application (version 1.5) was used in this study on a12.9 inches (2nd generation) iPad Pro with a screen resolution of 2732 × 2048. This screen size was chosen specifically as it allows for greater size and testing combinations that would be particularly useful in cases of visual impairment. The default screen brightness of 75% was used in this study (mean screen luminance: 194.9 ± 33.4 cd/m^2 (grey scale: 214.4 ± 11.3 cd/m^2), measured using Konica Minolta photometer (LS-110)). The iPad was switched on for at least 15 minutes prior to testing the first child in order for the screen luminance to stabilize. A uniform testing distance of 50 cm was used for all the participants (spatial frequency range: −0.18 to 1.9 logMAR). When the child's arm length was shorter than 50 cm, or if the child did not touch the screen themselves either due to unwillingness or restricted movements of the upper limbs, the examiner touched it based on the eye movement of the child or based on the direction in which the child was pointing, either to the right or left. When the correct touch response was given, an audio ('yippee') along with a video (cartoon) feedback popped up, thus engaging the child and motivating them to continue the test. In the event of an incorrect touch response there was no audio or video output. Only one examiner, the first author of this study tested all the participants. This examiner has over 10 years of experience of assessing visual acuity in children with a broad range of disabilities. The examiner held the iPad Pro in a landscape orientation and was not aware of the side to which the grating was displayed. Another examiner (referred to as the observer) was constantly present and helped in holding the tape measure to ensure that the working distance was maintained during testing. Although age-appropriate alternate forced-choice paradigm has been recommended by the developer, we decided to use a uniform 2-alternate forced-choice paradigm for all children so that it could be easily compared to Teller acuity cards II; it was also convenient to track eye movements in preverbal/nonverbal children. With four targets on a small screen, it is difficult to reliably ascertain where the child is looking and could potentially introduce greater response bias. The testing was initiated for all the children from 1.9 logMAR, instead of the default 1.3 logMAR to account for the fact that some children may have severe visual impairment (Harris, 2020). Peekaboo Vision follows the staircase method of presenting gratings with a three-line logMAR down and one-line logMAR up. However, for each incorrect response the same grating was presented two more times and the response that was obtained two out of three times for that particular grating was taken as the correct response.

Teller acuity cards II

Teller acuity cards II were used without the testing stage as this measurement was carried out as part of a vision screening camp and using the complete set-up was not feasible. Although reducing testing distance for children with visual impairment can be carried out if needed (TAC II: reference and instruction manual, 2005), in the current study, a uniform testing distance of 55 cms was used for all children to keep it similar to the assessment carried out with Peekaboo Vision application. The length of the card (55 cms) was used as a reference to ensure that the testing distance was maintained while presenting the cards prior to commencing the test. Descending order of limits paradigm was followed to present the cards. The spatial frequency ranged from 0.32 cycles per centimeter (CPCM) to 26.0 CPCM (~ to 1.97 logMAR to 0.08 logMAR). Each card was presented twice to verify the response. If the child gave a different response for the presentation of the card, then it was presented one more time and the response that was obtained two out of three times was considered to be the final response for that particular card. In case the child was not/incorrectly responding to a particular card two out of three times, then the card that was shown earlier was considered to be the end point of the test.

PROCEDURE

The presenting binocular visual acuity of children with Down syndrome was measured by the examiner (***Figure 1***). The sequence of tests were randomized prior to testing using a randomly generated table in Microsoft Excel. One examiner (author RS) conducted both the tests but was masked to the stimuli. This examiner was helped by an observer who kept a record of the observations and the presented stimuli. The observer also helped in timing the test duration (using a stopwatch), handing over the charts/replacing them and in noting down the child's responses as judged by the examiner. In addition to measuring presenting visual acuity a comprehensive vision screening

Figure 1 Grating acuity testing using Peekaboo Vision application.

was also carried out that included history taking, refraction, assessing accommodative status, anterior segment evaluation and undilated fundus evaluation (these results have not been included, as they are beyond the scope of this paper). Those children who were likely to benefit from a dilated/cycloplegic examination were referred to pediatric ophthalmologists in a tertiary eye care institute. Retest was attempted on children with Down syndrome and on controls within an average duration of 2.5 months. Verbal feedback about the child's engagement with Peekaboo Vision application was obtained from the parents.

STATISTICAL ANALYSIS

Data was analyzed using IBM SPSS software (ver. 20, Chicago, USA). Paired tests were used, either parametric or non-parametric depending on the normality distribution of the outcome measure, i.e., visual acuity. $p < 0.05$ was considered to be statistically significant. Limits of agreement (95%) between both tests were studied using Bland-Altman analysis.

RESULTS

Thirty-seven children with a confirmed diagnosis of Down syndrome and a control group of 28 chronologically age-matched children with normal developmental milestones and no obvious ocular abnormalities participated (***Table 1***). Presenting visual acuity was recorded with habitual correction in eight children with Down syndrome (21.6%) and no child in the control group wore spectacles.

DOWN SYNDROME

Testability rates were high and similar for both acuity tests (Peekaboo Vision and Teller acuity cards II = 97.2%). Mean acuity obtained using Peekaboo Vision and Teller acuity cards II was 0.16 ± 0.34 logMAR (range = −0.18 to 1.5) and 0.63 ± 0.34 logMAR (range = 0.08 to 1.55) respectively. A significant difference was obtained between these two tests ($p < 0.001$, paired sample t-test) with a mean difference in acuities of −0.44 ± 0.38 logMAR (95% LoA: −1.18 to 0.3) (***Figure 2a***). Peekaboo Vision overestimated acuity when compared to Teller acuity cards II by approximately 4.5 lines. Time taken to complete Peekaboo Vision (mean = 1.8 ± 0.8 min) and Teller acuity cards II (mean = 1.9 ± 0.8 min) was comparable ($p = 0.83$, paired sample t-test) in children with Down syndrome.

CONTROLS

Testability rates were high for both acuity tests (Peekaboo Vision and Teller acuity cards II = 100%). Mean acuity with Peekaboo Vision and Teller acuity

S NO.	DEMOGRAPHIC/CLINICAL PARAMETER	CHILDREN WITH DOWN SYNDROME (N = 37)	CONTROL GROUP (N = 28)
1	**Age (years)**		
	(Mean ± SD)	8.1 ± 4.2	8.71 ± 3.84
	Range	1.3 to 17.0	2.3–15.0
2	**Gender (n, %)**		
	Males	23 (62%)	15(54%)
	Females	14 (38%)	13 (46%)
3	**Testing duration (Mean ± SD) in minutes**		
	Peekaboo Vision	1.8 ± 0.8	1.17 ± 0.38
	Teller acuity cards II	1.9 ± 0.8	1.44 ± 0.49
	p-value	0.83	0.01

Table 1 Clinical and demographic characteristics of the participants.

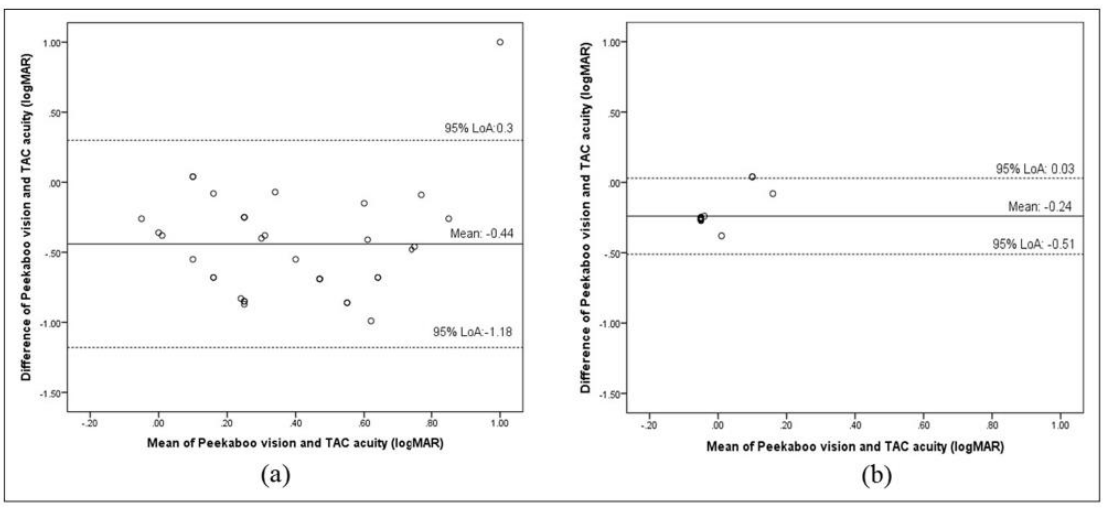

Figure 2 Bland-Altman plot representing 95% limits of agreement between acuity obtained using Peekaboo Vision and Teller acuity cards II in children with Down syndrome (n = 37) (2a) and in controls (n = 28) (*overlapping data points noted*) (2b).

cards II were −0.13 ± 0.12 and 0.12 ± 0.09 logMAR respectively. A significant difference in grating acuity was obtained in controls between these two tests ($p < 0.001$, Wilcoxon signed-rank test) with a mean difference in acuities of −0.24 ± 0.14 logMAR (95% LoA: −0.51 to 0.03 logMAR) (***Figure 2b***). Peekaboo Vision overestimated the acuity when compared to Teller acuity cards II by approximately 2.5 lines. Significantly less testing time ($p = 0.01$, paired-sample t-test) with Peekaboo Vision was noted (mean = 1.17 ± 0.38 min) in comparison to Teller acuity cards II (mean = 1.44 ± 0.49 min) in the control group.

As a follow-up to the vision screening program, only a small subset of children (n = 7) visited the tertiary eye care and participated in test-retest repeatability of the VA tests, despite attempts made to reach all the children referred for further examination through follow up telephone calls. Approximately three and half lines (CR = 0.35) (1.2 octave) variability was obtained with Peekaboo Vision [mean acuity difference: 0.13 ± 0.14 logMAR, 95% LoA (limits of agreement)] and above four lines (CR = 0.43) variability with Teller acuity cards II [mean acuity difference: −0.05 ± 0.23 logMAR, 95% LoA: −0.5 to 0.4] in children with Down syndrome. Fifteen controls also underwent retest and approximately three lines (CR = 0.33) (1.1 octave) variability with Peekaboo Vision [mean acuity difference: −0.02 ± 0.18 logMAR, 95% LoA: −0.37 to 0.33] and less than one line (CR = 0.08) variability [mean acuity difference: 0.00 ± 0.05 logMAR, 95% LoA: −0.1 to 0.1,] was noted with Teller acuity cards II.

The interactive video feedback in Peekaboo Vision app was found to be a useful feature. All parents (100%) across both groups felt that the interactive feedback was helpful in maintaining their child's attention whilst carrying out the test.

DISCUSSION

This is the first study to investigate the usefulness of a tablet-based, freely available application Peekaboo Vision for children with Down syndrome. Our findings suggest that there is potential to use Peekaboo Vision in measuring grating acuity in children with Down syndrome. Mean logMAR acuities obtained with Peekaboo Vision and Teller acuity cards II were found to be significantly different in children with Down syndrome (mean: −0.44 logMAR, 95% LoA: −1.18 to 0.3) and for controls (mean: −0.24logMAR, 95% LoA: −0.51 to 0.03) ($p < 0.001$). The present study's control group acuity findings were comparable to the acuity differences obtained between Peekaboo Vision application and Keeler acuity cards noted in the study by Livingstone et al. (Study 2: mean difference: 0.01 logMAR, 95% LoA: −0.413 to 0.437) that was carried out in typically developing children.

Some of the differences observed between the two tests may be related to their thresholding paradigms. Teller Acuity cards II uses the descending method of limits to present stimuli and responses obtained two out of three times were used to estimate grating acuity. The procedure is manual, and the step size (0.5 octave steps) may take longer before arriving at and refining the end point. Whereas, Peekaboo Vision uses an automated staircase paradigm which may be quicker and considerably more time efficient in arriving at the end point (Spielmann et al., 2013), this was evident in the control group in our study. A shorter testing time is desirable when assessing all children particularly non/preverbal and the younger age groups given their limited attention span. The difference could also be due to the larger jump in Peekaboo Vision acuity especially while thresholding at the finer grating acuity range (i.e., an incorrect response at −0.18 logMAR will have a 0.3 logMAR jump back to 0.12 logMAR) that accounts for an absolute difference of 0.3 logMAR. Another reason could be the uniform testing distance that was used for all age groups with Teller acuity cards II and Peekaboo Vision. According to the developer's guidelines, testing distance for Teller acuity cards II should be varied based on age (TAC II: reference and instruction manual, 2005). However, to standardize the tests, a similar testing distance was used for Teller acuity cards II and Peekaboo Vision, for all participants. Hence the highest spatial frequency that could be recorded using Teller acuity cards II in the current study was 0.08 logMAR, which could have caused an artificial ceiling effect particularly for the control group. Children with Down syndrome are noted to have hypoaccommodation. (Satgunam et al., 2019) The nature of the tests (print vs. digital) could have influenced the accommodation, differently. This was not investigated as part of this study.

High prevalence of refractive errors has been reported in children with Down syndrome (Akinci et al., 2009; Woodhouse et al., 1997). However, in the present study only 8 children with Down syndrome were noted to be spectacle users. Following the vision screening, those who needed refractive correction were prescribed spectacles and this data has not been reported here as it is beyond the scope of this paper.

Peekaboo Vision has several advantages over paper-based traditional visual acuity tests which are worthwhile to consider. It is easy to administer, is freely available and has high testability rates. Similar to Teller acuity cards II, 97% of children with Down syndrome and 100% of children in the control group were able to complete the test. It is also highly engaging, which would be particularly beneficial for children with special educational needs who tend to have a limited attention span. All parents of children who participated in the study gave positive feedback about the child's engagement with the app. Peekaboo Vision can measure a range of acuities that would be particularly desirable on a population of children with special educational needs, who may present with a range of acuities. For example, at 50 cm, acuity measured ranges from −0.18 to 1.9 logMAR. By alternating the working distance, the range can be further expanded to −0.18 to 2.11 logMAR. In addition, as Peekaboo Vision application has an automated threshold, it is easier for even a novice examiner to carry out the test as in comparison to the experience that is often recommended to perform the test using conventional paper-based cards (Getz et al., 1996). However, this may be challenging if an inexperienced examiner has to judge responses based on the eye movements of the child and 'touch' the screen for the child. Good eye-hand coordination is needed to perform the test using the Peekaboo Vision application. Children with special educational needs (e.g., with cerebral palsy) may have limited eye-hand coordination, which would make the task challenging. In such cases, the examiner should be able to judge the eye responses and touch the grating on behalf of the child.

Test-retest repeatability is an important measure to determine the clinical validity of any test (Sanchez and Binkowitz, 1999). Repeatability was noted to be within 1 octave (i.e., doubling/halving of the spatial frequency) using acuity card procedures (Mackie and McCulloch, 1995) in several studies in children with special educational needs, such as cerebral palsy (76%) (Hertz and Rosenberg, 1988), Down syndrome (73%) (Hertz, 1987), and other neurological conditions (88%) (Getz et al., 1996). A study by Livingstone et al. in 2019 on typically developing children using Peekaboo Vision reported approximately three lines variability in both studies, i.e., in Malawi and the United Kingdom (study 1: 95% LoA: −0.283 to 0.198 logMAR, CR = 0.27; study 2: 95% LoA: −0.344 to 0.320 logMAR, CR = 0.32), which corresponds to less than 1 octave and 1.1 octave respectively. This was comparable to the present study in controls. Due to poor follow-up, only a small number of children with

Down syndrome were recruited for a retest in this study which is a limitation.

The clinical testing of the Peekaboo Vision app in children with Down syndrome reveals comparable testing time similar to the well-established Teller acuity cards II and significantly shorter time in controls. In addition to the descending method of limits paradigm used for thresholding acuity using Teller acuity cards II, the mechanical shifting of the cards could also account for the longer testing time. A larger sample size would be needed to determine the test-retest repeatability of Peekaboo Vision in children with Down syndrome and other disabilities. This would not only prove useful in the regular clinical testing of children with disabilities but also to quantify the true effect of any intervention using grating acuity.

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FUNDING INFORMATION

Hyderabad Eye Research Foundation.

COMPETING INTERESTS

The authors have no competing interests to declare.

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A4. L V Prasad Eye Institute's Ethics Committee approval letter

Hyderabad Eye Research Foundation

World Health Organization
Collaborating Centre for Prevention of Blindness

L V Prasad Eye Institute Ethics Committee
Kallam Anji Reddy Campus, Banjara Hills, Hyderabad
ECR/468/Inst./AP/2013/RR-16

January 17, 2019 **Ethics Ref. No. LEC 01-19-205**

To:

Ms Rebecca Sumalini

Principal Investigator
L V Prasad Eye Institute
L V Prasad Marg, Banjara Hills
Hyderabad- 500 034
Telangana

Subject: Ethics Committee Approval Letter for Prospective Study

Protocol Entitled: "Validating clinical tools to measure visual functions in children with special needs"

Dear Ms Rebecca Sumalini:

With reference to your Submission for the approval of above protocol, the Institutional Review Board, L V Prasad Eye Institute, held on January 17, 2019 has reviewed and discussed the below mentioned list of documents submitted by you and approved the same.

Sl No	Documents
1.	Study Protocol
2.	Informed Consent Form

It is understood that the study will be conducted under your direction at L.V. Prasad Eye Institute, Hyderabad

It is hereby confirmed that neither you nor any of the members of the study team participated in the decision making/voting procedures. After consideration, the committee has approved the study for a period of one year. (Until closing hour of January 16, 2020)

We hereby confirm that, the Institutional Review Board, L V Prasad Eye Institute is organized and operates as per GCP (Good Clinical Practice) and applicable Indian regulations.

L V Prasad Eye Institute, Kallam Anji Reddy Campus, L V Prasad Marg, Banjara Hills, Hyderabad 500034, India
Tel: +91 40 30612345, Fax: +91 40 23548271, Email: info.hyd@lvpei.org, Website: www.lvpei.org

Please note:

a. In the events of any protocol amendments, Ethics Committee must be informed and the amendments should be highlighted. All approval of amendments in the projects must be obtained prior to implementation of changes. The amendment is unlikely to be approved by the Ethics Committee unless all the required information is provided.

b. Any advertisement placed in the newspapers, magazines must be submitted for approval.

c. The results of the study should be presented in any of the academic forums of the Institute.

d. Any SAE, which could affect any study, must be communicated to Ethics Committee within 24 hours of their occurrence and evaluate the rate of complications if any.

e. Any protocol deviation/ waiver in the protocol must be informed to the Ethics Committee

f. At the time of PI's retirement/intention to leave the institute, the study responsibility should be transferred to a colleague with an approval from the Ethics Committee

g. For extension of your study you are requested to submit the status (ongoing / closed etc) and progress reports (how many recruited, how many followed up and how many left the study etc.) by mail or hard copy to the Ethic Committee one month before completion of one year of the study period as given above. The decision for extensions would be taken by the Ethics Committee Members and conveyed to PIs in hard copies. Lack of response from PI's regarding the status/inadequate progress reports or no responses beyond deadline would be deemed as closure of the study by the EC and conveyed to the PI who would now have to present the study afresh in the next EC meeting. The EC would also take a decision for PI's who fail to submit progress reports on time and refrain the PI from presenting any further study to the EC until further notice or until reports are submitted and presented in person with reason for delay/ non-response.

Hyderabad Eye Research Foundation

World Health Organization
Collaborating Centre for Prevention of Blindness

L V Prasad Eye Institute Ethics Committee
Kallam Anji Reddy Campus, Banjara Hills, Hyderabad
ECR/468/Inst./AP/2013/RR-16

The following members of the Ethics Committee were present at the meeting held on January 17, 2019, 2018 at 3:00pm, Godrej Hall, Level VI, L V Prasad Eye Institute, KAR Campus, Hyderabad 500 034

Name	Qualification	Designation/Title	Gender	Affiliations as to the Institution Yes/No
[redacted]		Chair person and legal expert	Male	No
		Member Secretary	Male	Yes
		Theology & National Coordinator	Male	No
		Lay person	Female	Yes
		Basic Medical Scientist	Male	Yes
		Clinician	Female	No
		Basic Medical Scientist	Male	No

Thanking you

Yours Sincerely,

Ethics committee
L.V. Prasad Eye Institute
Kallam Anji Reddy , Campus
Banjara Hills, Hyderabad-500 034
Reg.No. ECR/468/Inst./AP/ 2013/RR-16

[redacted]

Member Secretary
L V Prasad Eye Institute Ethics Committee
L V Prasad Eye Institute, Banjara Hills
Hyderabad- 500 034

A5. L V Prasad Eye Institute's Ethics Committee study extension approval letter (latest)

Hyderabad Eye Research Foundation

L V Prasad Eye Institute Ethics Committee
Kallam Anji Reddy Campus, Banjara Hills, Hyderabad
Registration No: ECR/468/Inst./AP/2013/RR-19
DHR Registration No EC/NEW/INST/2021/TE/0021
NABH Registration No: EC-CT-2019-0126

To

Date: March 24, 2023

Dr Premnandhini Satgunam
Principal Investigator,
L V Prasad Eye Institute,
KAR Campus, L V Prasad Marg,
Banjara Hills, Hyderabad – 500 034,

Subject: Ethics Committee Approval for Extension of the study

Protocol Title: "Validating clinical tools to measure visual functions in children with special needs"

Ethics Ref No: LEC 01-19-205

Dear Dr Premnandhini Satgunam:

This is with reference to your request regarding an extension of the above ongoing mentioned study. The members reviewed and discussed in detail the progress report submitted by you, after consideration, the committee has approved the study for one more year.

It is hereby confirmed that neither you nor any of the members of the study team participated in the decision making/voting procedures.

We here by confirm that the Institutional Review Board, L.V Prasad Eye Institute is organized and operates as per GCP and Applicable Indian regulations

Ethics Committee
L. V. Prasad Eye Institute
Kallam Anji Reddy Campus,
Banjara Hills, Hyderabad-500 034
Reg.No.ECR/468/Inst./AP/2013/RR-19

LV Prasad Eye Institute, Kallam Anji Reddy Campus, L V Prasad Marg, Banjara Hills, Hyderabad 500034, India
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Hyderabad Eye Research Foundation

L V Prasad Eye Institute Ethics Committee
Kallam Anji Reddy Campus, Banjara Hills, Hyderabad
Registration No: ECR/468/Inst./AP/2013/RR-19
DHR Registration No EC/NEW/INST/2021/TE/0021
NABH Registration No: EC-CT-2019-0126

The following members of the Ethics Committee were present at the meeting held on Friday March 24, 2023 at 2:30pm via ZOOM, L V Prasad Eye Institute, KAR Campus, Hyderabad 500 034

Name	Qualification	Designation/Title	Gender	Affiliations as to the Institution Yes/No
[redacted]		Chairperson and Social Scientist	Male	No
		Member Secretary	Male	Yes
		Basic Medical Scientist	Male	Yes
		Basic Medical Scientist	Male	No
		Layperson	Female	Yes
		Clinician	Male	No
		Social Scientist	Female	No
		Legal Expert	Female	No

Yours Sincerely

[redacted]

Ethics Committee
L. V. Prasad Eye Institute
Kallam Anji Reddy Campus,
Banjara Hills, Hyderabad-500 034
Reg.No.ECR/468/Inst./AP/2013/RR-19

Member Secretary

L V Prasad Eye Institute Ethics Committee

L V Prasad Eye Institute, Banjara Hills, Hyderabad- 500 034

A6. City, University of London's Ethics Committee approval letter

Rebecca Chakram

Division of Optometry & Visual Sciences

School of Health Sciences

City, University of London

London

EC1V 0HB

27th of March 2019

REGISTRATION

Dear Rebecca,

Reference: ETH1819-0829

Project Title: Validating clinical tools to measure visual functions in children with special needs

Start Date: 1st of March 2019

End Date: 31st of January 2022

Thank you for uploading the relevant approval letter for an externally approved project.

The Principal Investigator must ensure that any relevant local governance policies and procedures are adhered to. You are now free to start recruitment.

Please ensure that you are familiar with City's Framework for Good Practice in Research and any appropriate Departmental/School guidelines.

Project amendments/extensions

Note that you must complete an amendment/extension form if one of the following occurs:

- Change or add a new category of participants;
- Change or add researchers involved in the project, including PI and supervisor;
- Change to the sponsorship/collaboration;
- Add a new or change a territory for international projects;
- Change the procedures undertaken by participants, including any change relating to the safety or physical or mental integrity of research participants, or to the risk/benefit assessment for the project or collecting additional types of data from research participants;

- Change the design and/or methodology of the study, including changing or adding a new research method and/or research instrument;
- Change project documentation such as protocol, participant information sheets, consent forms, questionnaires, letters of invitation, information sheets for relatives or carers;
- Change to the insurance or indemnity arrangements for the project;
- Change the end date of the project.

Adverse events or untoward incidents

- Adverse events;
- Breaches of confidentiality and/or inappropriate disclosure of personal data under GDPR;
- Safeguarding issues relating to children or adults at risk;
- Incidents that affect the personal safety of a participant or researcher.

Adverse events and breaches of confidentiality and/or inappropriate disclosure of personal data under GDPR should be reported as soon as possible and no later than five days after the event. Incidents that affect the personal safety of a participant or researcher and safeguarding issues relating to children or adults at risk should be reported immediately. You should also report adverse events to the relevant institutions, including police or social services.

As a condition of the sponsorship, the School reserves the right to audit compliance with the School Research Governance Framework. Further information on the audit process is available from the Chair of the School Research Ethics Committee.

Under the School Research Governance Framework you are required to contact Alison Welton once the project has been completed, and will be asked to complete a brief progress report 6 months/1 year after registering the project.

Kind regards,

[redacted]

School of Health Sciences Research Ethics Committee

City, University of London

Ms Rebecca Chakram

Optometry & Visual Sciences

School of Health & Psychological Sciences

City, University of London

London

EC1V 0HB

3rd of May 2023

REGISTRATION

Dear Rebecca,

Reference: ETH2122-1153

Project Title: Validating clinical tools to measure visual functions in children with special needs

Start Date: 1st of March 2019

End Date: 31st of March 2023

Thank you for uploading the relevant approval letter for an externally approved project.

The Principal Investigator must ensure that any relevant local governance policies and procedures are adhered to. You are now free to start recruitment.

Please ensure that you are familiar with City's Framework for Good Practice in Research and any appropriate Departmental/School guidelines.

Project amendments/extensions

Note that you must complete an amendment/extension form if one of the following occurs:

- Change or add a new category of participants;
- Change or add researchers involved in the project, including PI and supervisor;
- Change to the sponsorship/collaboration;
- Add a new or change a territory for international projects;
- Change the procedures undertaken by participants, including any change relating to the safety or physical or mental integrity of research participants, or to the risk/benefit assessment for the project or collecting additional types of data from research participants;

- Change the design and/or methodology of the study, including changing or adding a new research method and/or research instrument;
- Change project documentation such as protocol, participant information sheets, consent forms, questionnaires, letters of invitation, information sheets for relatives or carers;
- Change to the insurance or indemnity arrangements for the project;
- Change the end date of the project.

Adverse events or untoward incidents

- Adverse events;
- Breaches of confidentiality and/or inappropriate disclosure of personal data under GDPR;
- Safeguarding issues relating to children or adults at risk;
- Incidents that affect the personal safety of a participant or researcher.

Adverse events and breaches of confidentiality and/or inappropriate disclosure of personal data under GDPR should be reported as soon as possible and no later than five days after the event. Incidents that affect the personal safety of a participant or researcher and safeguarding issues relating to children or adults at risk should be reported immediately. You should also report adverse events to the relevant institutions, including police or social services.

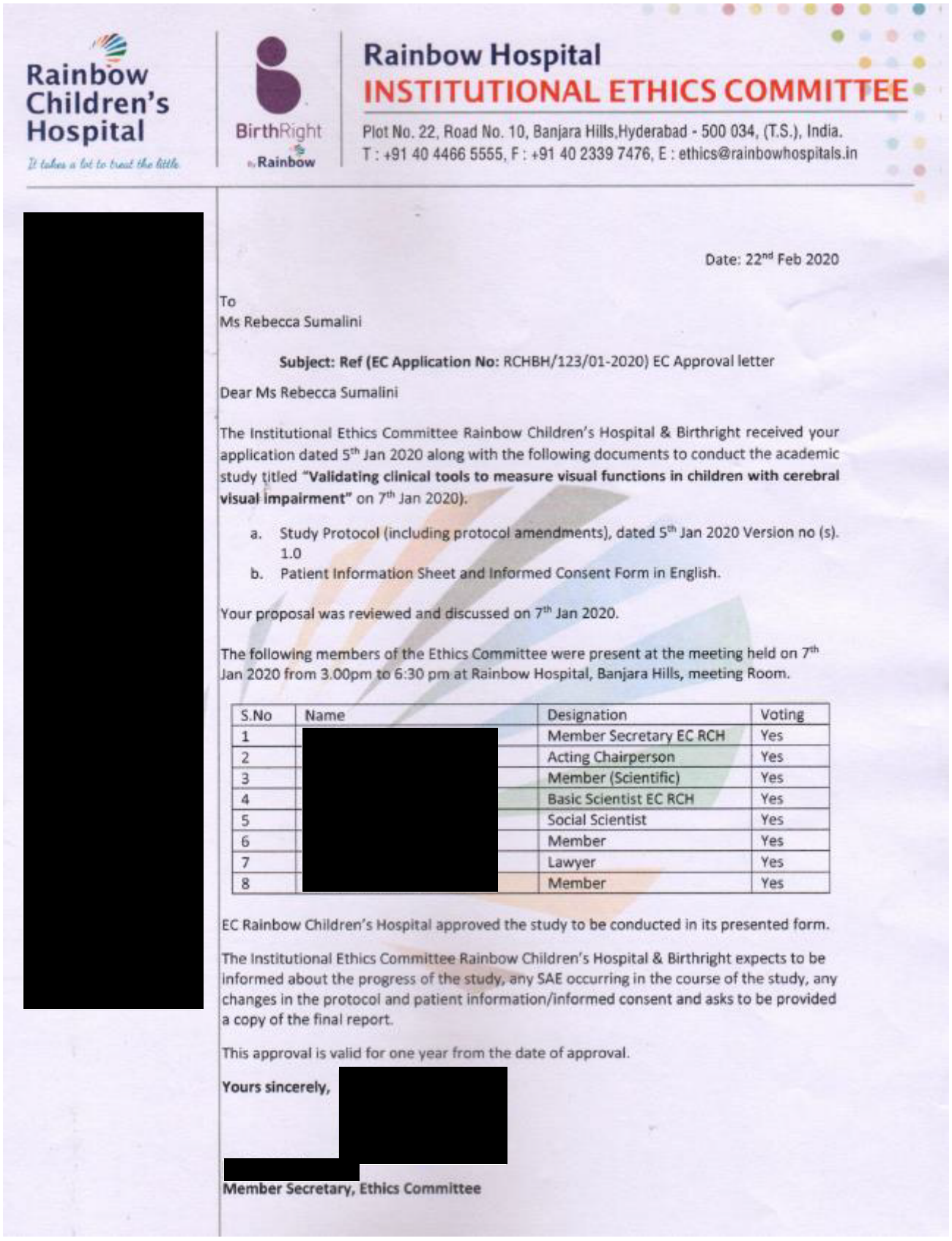
Kind regards,

[redacted]

Optometry Proportionate Review Committee

City, University of London

A7. Rainbow Children's Hospitals' Ethics Committee approval letter



Rainbow Children's Hospital
It takes a lot to treat the little.

BirthRight by Rainbow

Rainbow Hospital
INSTITUTIONAL ETHICS COMMITTEE

Plot No. 22, Road No. 10, Banjara Hills,Hyderabad - 500 034, (T.S.), India.
T : +91 40 4466 5555, F : +91 40 2339 7476, E : ethics@rainbowhospitals.in

[redacted]

Date: 22nd Feb 2020

To
Ms Rebecca Sumalini

Subject: Ref (EC Application No: RCHBH/123/01-2020) EC Approval letter

Dear Ms Rebecca Sumalini

The Institutional Ethics Committee Rainbow Children's Hospital & Birthright received your application dated 5th Jan 2020 along with the following documents to conduct the academic study titled **"Validating clinical tools to measure visual functions in children with cerebral visual impairment"** on 7th Jan 2020).

a. Study Protocol (including protocol amendments), dated 5th Jan 2020 Version no (s). 1.0
b. Patient Information Sheet and Informed Consent Form in English.

Your proposal was reviewed and discussed on 7th Jan 2020.

The following members of the Ethics Committee were present at the meeting held on 7th Jan 2020 from 3.00pm to 6:30 pm at Rainbow Hospital, Banjara Hills, meeting Room.

S.No	Name	Designation	Voting
1	[redacted]	Member Secretary EC RCH	Yes
2		Acting Chairperson	Yes
3		Member (Scientific)	Yes
4		Basic Scientist EC RCH	Yes
5		Social Scientist	Yes
6		Member	Yes
7		Lawyer	Yes
8		Member	Yes

EC Rainbow Children's Hospital approved the study to be conducted in its presented form.

The Institutional Ethics Committee Rainbow Children's Hospital & Birthright expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

This approval is valid for one year from the date of approval.

Yours sincerely,

[redacted]

Member Secretary, Ethics Committee

A8. Participant information sheet

Every child is special, but few children require extra attention as they have special needs for their eye care. The regularly used vision testing tools may not be helpful in measuring the different parameters due to their limited cooperation. Hence, there is a need to standardize the existing clinical protocols in examining and managing children with special needs. In this study, we will perform the visual tests on children and then analyse the results to validate the tests. The participation in the study is voluntary. By participating, your child may or may not be directly benefitted. But eventually, the outcomes of the study will be helpful to standardize the visual tests to be used on children with special needs and to measure the effectiveness of the rehabilitative interventions.

A9. Informed consent form

Date: 21.12.2018
Protocol Title: Validating clinical tools to measure visual functions in children with special needs
Principal Investigator: Rebecca Sumalini **Application No.:**

MR No.

Site of Research
L V Prasad Eye Institute, Kallam Anji Reddy campus, Hyderabad, India
National Institute for the Empowerment of Persons with Intellectual Disabilities, Hyderabad, India

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: Validating clinical tools to measure visual functions in children with special needs

Application No.:

Principal Investigator: Rebecca Sumalini

Date: 21.12.2018

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1. What you should know about this study?

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please read it carefully and take as much time as you need.
- Ask questions about anything you do not understand now, or when you think of them later.
- You are a volunteer. If you do join the study and change your mind later, you may quit at any time without fear of penalty or loss of benefits.
- While you are in this study, the study team will keep you informed of any new information that could affect whether you want to stay in the study.
- If children may join this study, the word "you" in this consent form will refer to both you and your child

2. Why is this research being done?

The primary purpose of this study is to validate the clinical tools for measuring visual functions in children with special needs. As there are no standardized protocols for assessing children with special needs, there is a need to validate the existing tools and later use them to measure the effectiveness of the rehabilitative interventions. Children with age 5 years and below with cortical visual impairment may join the study. In order to have an understanding of the test measurements for children who are normally sighted and with normal milestones, similar aged children who present without any visual complaints and have normal developmental milestones will also be recruited in the study.

Around 40 children with cortical visual impairment and around 40 children with normal developmental milestones will be enrolled into the study.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

- Read, understand and consent to participate in the study by signing the informed consent form
- You will be asked few questions about your child's medical history
- Your child's visual functions will be assessed using non-invasive equipment
- You will be asked about your child's day-to-day vision related performance

4. **What are the risks or discomforts of the study?**
It is unlikely to have any risks or discomforts associated with this study as it is totally non-invasive.

5. **Are there benefits to being in the study?**
There is no direct benefit to you by participating in this study. If you take part in this study, you may help others in the future.

6. **What are your options if you do not want to be in the study?**
You do not have to join this study. If you do not join, your care at L V Prasad Eye Institute will not be affected.

7. **Will it cost you anything to be in this study?**
The study procedures will be provided at no cost to you.

8. **Will you be paid if you join this study?**
No, you will not be paid or offered any financial rewards for joining in this study.

9. **Can you leave the study early?**
If you wish to stop, please tell us right away. Leaving this study early will not stop you from getting regular medical care. If you leave the study early, L V Prasad Eye Institute may use or give out your health information that it already has if the information is needed for this study or any follow-up activities.

10. **What information about you will be kept private and what information may be given out?**
L V Prasad Eye Institute has a policy to protect health information that may identify you. By signing this consent form, you agree that health information that identifies you may be used and/or given out as described in this form.

a. **What information about you may be used or given out in this study?**
Information that identifies you and relates to your health or medical condition may be used or given out as described in this form. Information that identifies you can include your name, medical record number, address, telephone number, date of birth, and other details about you.

b. **Who may use and give out information about you?**
Some people may see your health information and may give out your health information as needed to conduct this study. These people include the researcher and the research staff, the institutional review boards and their staff, legal counsel, audit and compliance staff, officers of the organization and other people who need to see the information to help this study or make sure it is being done as it should.

c. **Why will this information be used and given out?**
Your information will be used and given out to carry out this study and to evaluate the results of this study.

d. **What if you decide not to give your permission to use and give out your health information?**
You do not have to give your permission to use or give out your health information. However, if you do not give permission, you may not participate in this study.

e. **How long does this privacy authorization last?**
This authorization to use and give out health information does not end unless you cancel it. If you do this, you are leaving this study. If you leave this study, no new health information about you will

be gathered after the date that you leave. However, information gathered before that date may be used or given out if it is needed for this study or any follow-up for this study.

f. Is your health information protected after it has been given to others?
Even though L V Prasad Eye Institute has agreements with other organizations to protect the use of health information, if your health information is given to someone not covered by these policies and laws, that information may no longer be protected, and might be used or given out without your permission.

11. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?
The L V Prasad Eye Institute's IRB is made up of scientists, non-scientists, doctors and legal personnel. The IRB's purpose is to review human research studies and to protect the rights and welfare of the people participating in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 040-30612511.

b. What do you do if you have questions about the study?
Call the principal investigator, Ms. Rebecca Sumalini at 040-30612823.

c. What should you do if you are injured or ill as a result of being in this study?
If you have an urgent medical problem related to your participation in this study, call Dr. Archana Bhargava at 040-30612330.

If you think you are injured or ill as a result of being in this study, call the principal investigator, Ms. Rebecca Sumalini at 040-30612823.

The medical services at L V Prasad Eye Institute will be open to you as they are to all sick or injured individuals. L V Prasad Eye Institute does not have a program to pay you if you are hurt or have other bad results from being in the study. You are financially responsible for payment of any treatment or hospitalization. At your request, your insurance provider will be billed for payment of any treatment or hospitalization.

d. What happens to data that is collected in the study?
L V Prasad Eye Institute is dedicated to finding the causes and cures of ocular diseases. The data, collected during this study are important to this study and to future research. If you join this study, L V Prasad Eye Institute or its outside partners in this research will own this data. This material will be studied, tested and used by medical scientists. If this material helps lead to the creation of a product or idea, whoever creates that product or idea will own it. You will not receive any financial benefit from the creation, development, use or sale of that product or idea.

e. What are the Organizations that are part of L V Prasad Eye Institute?
L V Prasad Eye Institute is a group of hospitals that includes: L V Prasad Eye Institute, Hyderabad; The International Center for Advancement of Rural Eye Care (ICARE), Hyderabad; Bhosle Gopal Rao Patel Eye Center, Mudhole; Kuchakulla Ramachandra Reddy Eye Center, Thoodukuruthy; Venkatalakshmi Eye Center, Karamchedu; Siloam Eye Hospital, Madenapalle and Sheshanna Chennawar Eye Center, Adilabad etc.

12. What does your signature on this consent form mean?
By signing this consent form, you are not giving up any legal rights. Your signature means that you understand the information given to you in this form, you accept the provisions in the form, and you agree to join the study.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

Ethics committee
L.V. Prasad Eye Institute
Kallam Anji Reddy , Campus
Banjara Hills, Hyderabad-500 034
Reg.No. ECR/468/Inst./AP/ 2013/RR-16

Do not sign after the expiration date of: _____

FOR ADULTS AND CHILDREN CAPABLE OF GIVING CONSENT:

_____

Participant's caregiver's signature Date

SIGNATURE(S):

_____

Signature of Person Obtaining Consent Date
(Investigator or IRB Approved Designee)

_____

Witness to Consent Procedures (Optional unless IRB or Sponsor required) Date

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; AND, IF APPROPRIATE, A COPY OF THE CONSENT FORM MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD.

FOR OFFICE USE ONLY:
STUDY APPROVED FOR ENROLLMENT OF: ___ Adults Only ___ Adults and Children ___ Children Only

A10. Data recording sheet

S no.	Demographic data	
1	Subject no.	
2	Subject name	
3	Visit date	
4	Medical record no.	
5	Hospital	RCH (1) LVPEI (2)
6	Month and year of birth	
7	Gender	
8	Location	

S no.	Clinical data	
1	Aetiology of CVI	
	Diagnosis is based on	
2	Additional ocular diagnoses	
3	Additional neurological diagnoses	
	Associated features and its treatment	Microcephaly/Seizures/Others If seizures: Epileptic seizures/infantile spasms/jerks Last episode of seizures: On medications: Yes/No. If yes: Medications for attention /others: Yes/No If yes:

4	Birth history	Birth weight= _____ kgs Birth cry: Yes/No Term: Full-term/preterm/post term Gestational age: _____ weeks Route: Vaginal/Caesarean/others Neonatal jaundice: Yes/No Neonatal hypoglycaemia: Yes/No Pneumonia: Yes/No APGAR score: Maternal health concerns: Vaccinations: as per schedule (1), delayed (2), not given (3)
5	Developmental history	Height: Weight: BSA: BMI (kg/m^2): HC (cms): Percentile Milestones Motor: Speech: Cognition:
6	Chief complaints (overall development)	
7	Chief visual related complaints	
8	Additional comments	

S no.	Clinical and diagnostic tests	
1	MRI (date of the imaging test)	Impression: Grading:
2	EEG Visit 1 (date): Visit 2 (date): Medication change:	
3	Developmental quotient	

Visual acuity tests	
With TAC-II	OU: Time taken: Engagement score: 0 - no meaningful results) 1 - some meaningful results but loss of interest during test) 2 - engagement to convincing threshold or finest grating. To ask parents: Child fatigue/boredom: Will the child like to do the test again?
With PV app	OU: Time taken: Engagement score: 0 - no meaningful results) 1 - some meaningful results but loss of interest during test) 2 - engagement to convincing threshold or finest grating. To ask parents: Child fatigue/boredom: Will the child like to do the test again?
Sequence of test	PV and then TAC-II (1) / TAC and then PV (2)
Remarks	

Contrast sensitivity tests	
With Hiding Heidi cards	OU: Time taken: Engagement score: 0 - no meaningful results) 1 - some meaningful results but loss of interest during test) 2 - engagement to convincing threshold or finest grating. To ask parents: Child fatigue/boredom: Will the child like to do the test again? Yes/No
With Ohio contrast cards	OU: Time taken: Engagement score: 0 - no meaningful results) 1 - some meaningful results but loss of interest during test) 2 - engagement to convincing threshold or finest grating. To ask parents: Child fatigue/boredom: Will the child like to do the test again? Yes/No
Sequence of test	OCC and then HH (1) / HH and then OCC (2)
Remarks	

Other visual tests	
Retinoscopy (Dry)	OD: OS:
Acceptance	OD: OS:
Accommodation status (dynamic retinoscopy)	OD: OS:
Visual fields (gross)	
Ocular motility	
Binocular vision status	Squint: Nystagmus:
Anterior segment evaluation (SLE/TLE)	
Posterior segment evaluation	
Remarks	

A11. Video analysis form

1	Subject no.	
2	Date	

With TAC-II	Card no.: Would you have estimated the acuity threshold one card before than the last card shown or would you go beyond the last card shown? Card before (1) / Card beyond (2) / same card (3)
Remarks	

A12. Control data form

S no.	Demographic data	
1	Subject no.	
2	Date of birth	
3	Gender	
4	Chief visual related complaints	

	TAC-II	PV app	OKKO-VA
OU: Time taken: Engagement score: 0 - no meaningful results 1 - some meaningful results but loss of interest during test 2 - engagement to convincing threshold or finest grating.			
Sequence of tests			
	OCC	**HH cards**	**OKKO-CS**
OU: Time taken: Engagement score: 0 - no meaningful results 1 - some meaningful results but loss of interest during test 2 - engagement to convincing threshold or finest grating.			
Sequence of tests			

Squint	
Anterior segment examination	
Additional comments	

A13. Denver Developmental Screening Test-II

Name: **Age:**

Date:

GROSS MOTOS					
S.NO	ITEMS		1st ASSESSMENT	2nd ASSESSMENT	3RD ASSESSMENT
1	Equal movements	15 days			
2	Lift head	15 days			
3	Head up 45 degree	2m 15 days			
4	Head up 90 degree	3m 15 days			
5	Sit- head steady	4 months			
6	Bear weight on legs	4m 15 days			
7	Chest up arms support	4m 15 days			
8	Roll over	5m 15 days			
9	Pull to sit-No head-leg	6 months			
10	Sit no support	6m 15 days			
11	Stand holding on	8m 15 days			
12	Pull to stand	9m 15 days			
13	Get to sitting	10 months			
14	Stand 2 secs	11m 15 days			
15	Stand alone	13m 15 days			
16	Stoop and recover	14m 15 days			
17	Walks well	15 months			
18	Walk backward	1 4 ½ months			
19	Runs	1y 8month			
20	Walks up steps	1y 9 ½ months			
21	Kick ball forward	1y 11 months			
22	Jump up	2y 4 ½ months			
23	Throw ball over head	2y 11 months			
24	Broad jump	3y 1 ½ month			
25	Balance each foot 1 sec	3y 4months			
26	Balance each foot 2 sec	3y 11 months			
27	Hops	4y 3 months			
28	Balance each foot 3 sec	4y 7 ½ months			
29	Balance each foot 4 sec	5y 1 month			
30	Balance each foot 5 sec	5y 6 months			
31	Heel to toe walk	5y 8 months			
32	Balance each foot 6 sec	6 years			

LANGUAGE					
S.NO	ITEMS		1st ASSESSMENT	2nd ASSESSMENT	3RD ASSESSMENT
1	Sponds to bell	10 days			
2	Vocalize	20 days			
3	OOO/AAH	2m 15 days			
4	Laughs	3 months			
5	Squeals	4m 10 days			
6	Turns to rattling sound	5 ½ months			
7	Turn to voice	6 ½ months			
8	Single syllables	7m 10 days			
9	Imitate speech sounds	8m 20 days			
10	Dada/mama, non-specific	9 months			
11	Combine syllables	10 months			
12	Jabbers	12 months			
13	Dada/mama specific	13 ½ months			
14	One word	15 months			
15	Two words	16 ½ months			
16	Three words	18 months			
17	Six words	21 ½ months			
18	Point 2 pictures	23 ½ months			
19	Combine words	24 ½ months			
20	Name one picture	25 months			
21	Body parts-6	2y 4 ½ months			
22	Point 4 pictures	2y 7 months			
23	Speech half understandable	2y 11 months			
24	Name 4 pictures	2y 11 months			
25	Know 2 actions	3y 1 ½ months			
26	Know 2 adjectives	3y 7 months			
27	Name 1 color	3y 8 months			
28	Use of 2 objects	3y 9 months			
29	Count 1 block	3y 11 months			
30	Use of 3 objects	4y 1 month			
31	Know 4 actions	4y 2 months			
32	Speech all understandable	4y 3 months			
33	Understand 4 prepositions	4y 8 months			
34	Name 4 colors	4y 9 months			
35	Define 3 words	5y 4 months			
36	Know 3 adjectives	5y 4 ½ months			
37	Count 5 blocks	5y 4 ½ months			
38	Opposite 2	5y 8 months			
39	Define 7 words	6 years			

FINE MOTOR					
S.NO	ITEMS		1st ASSESSMENT	2nd ASSESSMENT	3RD ASSESSMENT
1	Follow to midline	1m 8 days			
2	Follow past Midline	2m 20 days			
3	Grasp rattle	3m 20 days			
4	Hands together	4 months			
5	Follow 180 degree	4 ½ months			
6	Regard raising	5 ½ months			
7	Reaches	6 ½ months			
8	Look for yarn	7m 6 days			
9	Rake raising	7m 8 days			
10	Pass cube	7m 20 days			
11	Take 2 cubes	9m 5 days			
12	Thumb finger grasp	10m 5 days			
13	Bang 2 cubes held in hand	11 months			
14	Put block in cup	13m 20 days			
15	scribbles	16m 10 days			
16	Dump raisin demonstrated	19 ½ months			
17	Tower of 2 cubes	20 ½ months			
18	Tower of 4 cubes	23m 20 days			
19	Tower of 6 cubes	2y 7 ½ months			
20	Imitative vertical line	3y 3 months			
21	Tower of 8 cubes	3y 5 ½ months			
22	Thumb wiggle	3y 7 ½ months			
23	Copy O (circle)	4 years			
24	Draw person 3 parts	4y 7 ½ months			
25	Copy + (plus)	4y 8 ½ months			
26	Pick longer line	5y 3 months			
27	Copy square (demonstrate)	5y 5 ½ months			
28	Draw persons 6 parts	5y 6 months			
29	Copy square	6 years			

PERSONAL – SOCIAL					
S.NO	ITEMS		1st ASSESSMENT	2nd ASSESSMENT	3RD ASSESSMENT
1	Regard face	1 month			
2	Smile responsively	1m 10 days			
3	Smile spontaneously	2 months			
4	Regard own hand	4 months			
5	Work for toy	5m 20 days			
6	Feed self	6m 10 days			
7	Play pat – A – cake	11m 10 days			
8	Indicate wants	12m 20 days			
9	Wave bye - bye	14 months			
10	Play ball with examiner	15m 20 days			
11	Imitate activities	16months			
12	Drink from cup	17 months			
13	Help in house	17 m 10 days			
14	Use spoon/fork	20 months			
15	Remove garment	23m 20 days			
16	Feed doll	24 months			
17	Put on clothes	2y 6 months			
18	Brush teeth with help	2y 8 months			
19	Wash and dry hands	3y 15 days			
20	Name friend	3y 1 month			
21	Put on T-shirt	3y 4 ½ months			
22	Dress, no help	4y 5 months			
23	Play board/card game	4y 10½months			
23	Brush teeth, no help	5 years			
25	Prepare cereal	5y 1 month			

TOTAL SCORE

Developmental quotient (DQ) =

A14. CVI range instrument

S No.	CVI characteristics	Range 1-2 (0)	Range 3-4 (0.25)	Range 5-6 (0.50)	Range 7-8 (0.75)	Range 9-10 (1.00)
1	**Color preference**	Objects viewed are generally a single color	Has favourite color	Objects may have two to three favoured colors	More colors, familiar patterns regarded	No color or pattern preferences
2	**Need for movement**	Objects viewed generally have movement or reflective properties	More consistent localization, brief fixations on movement and reflective materials	Movement continues to be an important factor to initiate visual attention	Movement not required for attention at near	Typical responses to moving targets
3	**Visual latency**	Prolonged periods of visual latency	Latency slightly decreases after periods of consistent viewing	Latency present only when child is tired, stressed or overstimulated	Latency rarely present	Latency resolved
4	**Visual field preferences**	Distinct field dependency	Shows visual field preferences	Field preferences decreasing with familiar inputs	May alternate use of right and left fields	Visual fields unrestricted
5	**Difficulties with visual complexity**	Responds only in strictly controlled environments. Generally, no regard of the human face.	Visually fixates when environment is controlled	Regards familiar faces when voice does not compete	Competing auditory stimuli tolerated during periods of viewing.	Only the most complex visual environment affect visual response.
6	**Light-gazing and non-purposeful gaze**	May localize briefly, but no prolonged fixations on objects or faces. Overly attentive to lights or perhaps ceiling	Less attracted to lights; can be redirected to other targets.	Light is no longer a distractor		

		fans.				
7	**Difficulty with distance viewing**	Visually attends in near space only	Occasional visual attention to familiar moving, or large targets at 2 to 3 feet	Visual attention extends beyond near space, up to 4 to 6 feet	Visual attention extends to 10 feet with targets that produce movement	Visual attention extends beyond 20 feet demonstrates memory of visual events
8	**Atypical visual reflexes**	No blinks in response to touch and/or visual threat	Blinks in response to touch, but response may be latent	Blink response to touch consistently present (both reflexes near 90 percent resolved)	Visual threat response consistently present (both reflexes near 90 percent resolved)	Visual reflexes always present; resolved
9	**Difficulty with visual novelty**	Only favourite or known objects elicit visual attention	May tolerate novel objects share characteristics of familiar objects	Use of 'known' objects to initiate looking sequence	Selection of objects less restricted, one to two sessions of 'warm up' time required	Selection of objects not restricted
10	**Absence of visually guided reach**	Look and touch occur as separate functions. Look and touch occur with large and /or moving objects	Look and touch occur with smaller objects that are familiar, lighted, or reflective look and touch are still separate	Visually guided reach used with familiar objects or 'favourite' color	Look and touch occur in rapid sequence, but not always together	Look and touch occur together consistently

Total score= _____

Phase I: Building visual behaviour (score: 0-3)

Phase II: Integrating vision with function (3.25-7)

Phase III: Resolution of CVI characteristics (7.25-10.0)

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ORIGINAL RESEARCH

Parent-Reported Visual Concerns in Children with Cerebral Visual Impairment Presenting to a Pediatric Neurology Clinic

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Purpose: Children with cerebral visual impairment (CVI) present with delayed developmental milestones. Pediatricians and pediatric neurologists are usually the first point of contact, and eye exam largely remains referral based. This study documented the visual concerns reported by parents of children with CVI visiting a pediatric neurology clinic. Additionally, we investigated the association between visual concerns, functional vision measures and visual functions.

Patients and Methods: A cross-sectional study was undertaken in children with CVI (chronological age range: 7 months-7 years). Visual concerns reported by the parents/caregivers were documented as open-ended statements. Additionally, a functional vision assessment was conducted using the CVI Range instrument with phase 1, 2 and 3 indicating low, moderate and high visual functioning, respectively. Grating acuity and contrast sensitivity were measured using Teller acuity cards-II and Ohio contrast cards respectively.

Results: A total of 73 children (mean age of 2.84 ± 1.87 years) were recruited. Sixty-eight parents reported visual concerns that were broadly grouped into 14 unique concerns. Nineteen parents (27.9%) reported more than one visual concern. Difficulty maintaining eye contact and recognizing faces were the top two visual concerns in phases 1 and 2. Missing objects in the lower visual field was the top concern in phase 3. A larger number of visual concerns were reported in phase 1 (43%) than phase 2 (40.6%) and phase 3 (16.2%). Multiple regression analysis revealed that grating acuity, contrast sensitivity and chronological age were able to predict the functional vision, $F(3, 55) = 63.0$, $p < 0.001$, $r^2 = 0.77$.

Conclusion: Targeted questions enquiring about eye contact and face recognition can be included in history elicitation in children with CVI in pediatric neurology clinics. In the presence of visual concerns, it will be important to assess grating acuity and contrast sensitivity. A poor functional vision score requires referral for eye examination and vision rehabilitation services.

Keywords: functional vision, neurological visual impairment, CVI range, Teller acuity cards-II, Ohio contrast cards

Introduction

Cerebral visual impairment (CVI) is a neurological visual impairment that arises due to damage to the retro-geniculate visual pathways and can involve both cortical and sub-cortical regions of the brain.[1] Children with CVI not only present with typical functional vision limitations as observed in children with ocular visual impairment but additionally have difficulty with visual processing skills.[2] These children can also have developmental delays in one or multiple areas such as motor, speech, cognition, hearing and vision depending on the location and severity of the brain damage.[3] Therefore, in line with other healthcare sectors such as general health[4] or specific health issues,[5,6] parent/caregiver concerns form an integral basis for history taking and are helpful in deciding appropriate interventions and referral.

Children with CVI are more likely to first present to a pediatric or pediatric neurology clinic rather than an ophthalmology clinic as many of these children suffer from seizures and developmental delays which are more obvious

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than vision problems. A typical pediatric neurology history also covers vision concerns, but usually this is under the sub-section of headache.[7] In a small minority of cases where there are obvious vision problems such as poor eye contact, parents may directly visit an ophthalmology clinic first, but for a vast majority of children visits to the eye clinics are referral based. The referral for vision testing is largely left at the discretion of the pediatrician/pediatric neurologist based on their observations (such as fixing and following light) and concerns reported by the parents/caregivers. The inability to capture visual concerns appropriately is likely to lead to a missed referral diminishing the opportunity for early intervention in the domain of visual rehabilitation. As the overall development of the child and the learning process is dependent on vision (close to 80%),[8–11] it is be important to characterize these concerns.

The primary aim of this study is to determine the commonly reported parental concerns of children's functional vision limitations when presenting to a pediatric neurology clinic following a diagnosis of CVI. The secondary aims are to understand the association between parent reported vision concerns and functional vision assessment using the CVI Range, which is a well-established tool to quantify the functional vision assessment of children with CVI.[12] Additionally, we determine the association of functional vision assessment with commonly measured clinical visual functions (visual acuity and contrast sensitivity). Both parameters have been noted to play a vital role in day-to-day functional vision activities.[13]

Materials and Methods

A prospective, cross-sectional study was carried out in the pediatric neurology clinic of Rainbow children's hospitals, a tertiary multi-disciplinary pediatric hospital located in Hyderabad, Telangana, India. This work is a part of a larger study being carried out by the research group consisting of collaborators from L V Prasad Eye Institute, Hyderabad, India, Rainbow Children's Hospitals, Hyderabad, India, and City, University of London, London, UK, on children with CVI. Ethics approval was obtained from all three participating organizations, and the study followed the tenets of the Declaration of Helsinki. For the purpose of this study, parental concerns are reported.

Participants

Study participants were children (in the age range of 7 months to 7 years) diagnosed with CVI by the pediatric neurologist (author LL) based on magnetic resonance imaging scans of the brain, medical history and general observation of visual behaviour such as fixing and following light as is commonly practiced in these clinics. While the diagnostic criteria for CVI varies and remains broad,[14] studies have shown that a contributory medical history (pre- or peri-natal history) and an abnormal MRI are strong risk factors for diagnosing CVI.[15,16] Ideally, a complete ophthalmological examination will be needed to rule out anterior visual pathway defects. However, currently in pediatric neurology clinics, the diagnosis is made using MRI scans, medical history and general observation of visual behaviour and therefore the same diagnostic criteria were used in the current study. Informed written consent was obtained from the parents of the participating child. Verbal assent was obtained from children who were able to comprehend.

Instruments

Parental concerns about the functional vision limitations of the child were asked as an open-ended question, "What are the vision-related problems that you have noticed in your child?" without any specific leads or prompts. All visual concerns were recorded. No structured questionnaire was used for collecting this information.

Assessment of Functional Vision

Functional vision scoring was carried out using the CVI Range instrument, a commonly used functional vision scale designed for children with CVI.[12] The ten characteristics that are included in the CVI Range are listed in Table 1. All characteristics were assessed as recommended[12] through examiner observation, parent interview and direct assessment.[17] Each characteristic is graded separately, and the total score is the summation of the score obtained on all characteristics and can lie between 0.0 and 10.0 with a higher value indicating better functional vision. Based on the total score, the child is categorized into one of the three phases, phase 1 = building visual behavior (score range: 0 to 3.0), phase 2 = integrating vision with function (3.25 to 7.0) and phase 3 = resolution of CVI characteristics (7.25 to 10.0). The CVI

Table 1 The Ten Common Characteristics Observed in Children with CVI: The CVI Range Instrument[12]

Characteristics of the CVI Range Instrument	
1. Color preference	6. Light-gazing and non-purposeful gaze
2. Need for movement	7. Difficulty with distance viewing
3. Visual field preference	8. Atypical visual reflexes
4. Visual latency	9. Difficulty with visual novelty
5. Difficulty with visual complexity	10. Absence of visually guided reach

Abbreviation: CVI, cerebral visual impairment.

Range is usually administered through two ratings (i) across-the-characteristics scale (an overall understanding of the child's visual abilities) and (ii) within-the-characteristics scale (rating of each characteristic to understand the extent of the individual contribution to the overall visual functioning of the child).[12] Due to time constraints in assessing both ratings, we restricted our assessment to "within-the-characteristics" scale.

Assessment of Grating Acuity

Teller acuity cards-II (TAC-II)[18] were used to assess binocular presenting grating acuity. This test follows a preferential looking paradigm and is a 2-alternate forced choice (2-AFC) test. The gratings are vertically oriented. As the chronological age range of the children was 7 months and above, the first card was presented at 55 cms and then the decision to continue at the same testing distance or moving closer/farther was taken depending on the response of the child. As this cohort consists of children with visual impairment, the closest working distance used was 19 cms.[18] The length of the card (55 cms) was used as a reference to ensure that the testing distance was maintained while presenting the cards. The descending method of limits (from the lowest to the highest spatial frequency) paradigm was used to threshold the grating acuity with the examiner being masked to the grating location (as the cards were arranged upside down) until obtaining the child's response. The spatial frequency that can be measured using TAC-II from the closest testing distance of 19 cms is 0.23 cycles per centimeter (CPCM) (0.07 CPD) to farthest testing distance of 84 cms is 38.0 CPCM (57.0 CPD) (~2.63 to −0.27 logMAR). If the response to one card was incorrect (i.e. the child was looking or pointing to the blank side of the cards), then the same card was presented one more time and the response that was obtained two out of three times was considered to be the final response for that particular card. In case the child was not/incorrectly responding to a particular card two out of three times, then the card that was presented earlier was considered to be the end point of the test.

Assessment of Contrast Sensitivity

Ohio contrast cards[19] were used to assess binocular presenting contrast sensitivity. Similar to TAC-II, these cards also follow the preferential looking paradigm with a 2-AFC test but use horizontally oriented gratings. All children were tested at 57 cm,[19] which was used as an easy reference as it was the length of the card. Twelve contrast sensitivity levels can be measured using the Ohio contrast cards, i.e. from 100% to 2.2%. Thresholding paradigm of descending method of limits (i.e. from the easily identifiable contrast level to the difficult to identify contrast level) was used, and the examiner was masked to the location of the grating until obtaining the child's response. Additionally, the estimation technique was used to arrive at the threshold contrast level similar to that described above for TAC-II.

Eliciting the visual concerns of the children from the parents/caregivers, and the tests of visual functions were carried out by a single examiner (author RS). The assessment of functional vision was carried out by the author RS with the assistance of a trained vision rehabilitation professional (author PE).

Statistical Analysis

Data was analyzed using IBM SPSS software (ver. 20, Chicago, USA). Pearson chi-square was used to determine the significance in frequency distributions of visual concerns in the different phases of CVI. Spearman-rho was used to test the correlation between functional vision and visual functions. Kruskal-Wallis test was used to determine the statistical significance of visual functions across the 3 phases of CVI and across the chronological age categories. Multiple regression analysis was carried out to determine the parameters that best predict the functional vision score.

Results

A total of 73 children (mean age: 2.84 ± 1.87 years, range: 7 months–7 years, 74% males (n = 54)) with CVI were recruited. Only a small minority of children previously underwent an eye examination (n = 11, 15%) and in addition comprehensive eye evaluation findings carried out as part of a larger study were available in 10 children (13.6%). In the total 21 children (28.7%) in whom these findings were available, optic atrophy was noted to be the most common ocular abnormality (n = 14, 66.6%), followed by normal fundus findings in 6 children (28.5%) and 1 child who had retinopathy of prematurity (4.7%). All the children had abnormal MRI findings, including 2 children who had genetic aetiology of CVI.

Five parents (6.8%) did not report any specific visual concerns, while the remaining (n = 68) did. Nineteen parents (27.9%) reported two visual concerns, giving rise to a total of 87 visual concerns documented from all participants. The reported visual concerns could be grouped into 14 unique visual concerns (Figure 1).

Functional Vision Assessment and Visual Concerns

One child (crying constantly) could not be assessed using the CVI range instrument. The remaining children (n = 72) were categorized into 3 phases based on their CVI range score (a higher score indicates better functional vision) (phase 1, n = 30 (41.6%); phase 2, n = 27 (37.5%), phase 3, n = 15 (20.8%)). The frequency distribution of all the visual concerns (including no visual concerns, n = 5) was found to be significantly different across all 3 phases of CVI (p = 0.012, Pearson chi-square). The distribution of the concerns across the phases is shown in Figure 1. The frequency distribution of visual concerns in individual phases: phases 1 and 2 (p = 0.46, Pearson chi-square), phases 2 and 3 (p = 0.06, Pearson chi-square) was found to be comparable, however, phases 1 and 3 were found to be significantly different (p = 0.012, Pearson chi-square). Among the 19 children whose parents reported more than one visual concern, the distribution of them in the phases was as follows: phase 1, n = 7 (36.8%); phase 2, n = 9 (47.3%); phase 3, n = 3 (15.7%).

Difficulty in recognizing faces (phase 1, n = 12 (40%); phase 2, n = 10 (37%)) and maintaining eye contact (phase 1, n = 9 (30%); phase 2, n = 12 (44.4%)) were noted to be the most common visual concerns in phases 1 and 2. The third

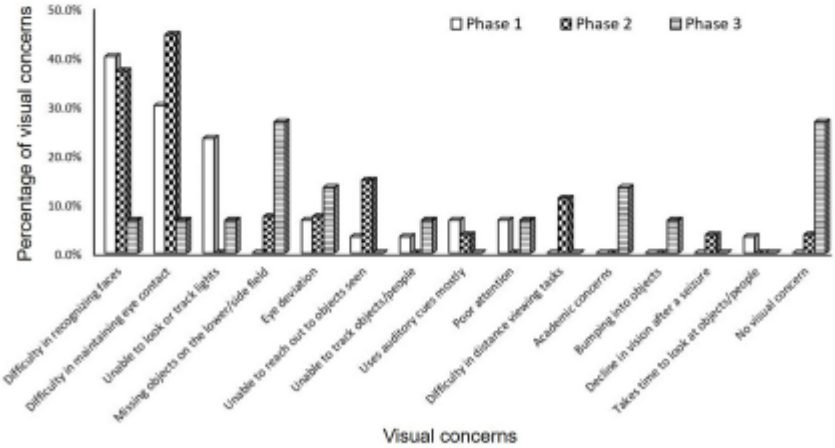

Figure 1 Clustered bar-graph representing the frequency distribution of both visual and no visual concerns based on the three phases of cerebral visual impairment (n = 72).
Note: Visual concerns are more in number than the sample, as some parents (n = 19) reported more than one visual concern.

highest visual concern of unable to look or track lights primarily was found in phase 1 (n = 7, 23.3%). Children in phase 3 (i.e. those who had better function) primarily had concerns with missing objects in the lower/side field (n = 4, 26.7%) (Figure 1 and Table 2).

As face recognition and eye contact were reported as the top two visual concerns overall, further analysis was carried out based on the functional vision. Functional vision of children whose parents reported difficulty with face recognition and eye contact (considered as group 1) was compared against those whose parents reported other visual concerns (considered as group 2). Children in group 1 were noted to be significantly younger (mean: 2.25 ± 1.55 years,

Table 2 Distribution of Children Across the 3-Phases of CVI Along with Chronological Age Categories, Visual Functions and Visual Concerns

CVI Range	Age Categories	Number of Children (n = 72)	Grating Acuity (Mean logMAR, Range)	Contrast Sensitivity (Mean logCS, Range)	Visual Concerns (n)*
PHASE 1 (n = 30)	7m–1 yr	7	2.25±0.85 (range: 2.30 to 2.13) (Does not appreciate demoplate=2)	0.00±0.00 (Does not appreciate demoplate=1, not testable=2)	Recognizing faces=3 Eye contact=2 Eye deviation=1 Unable to reach out to objects seen=1 Poor attention=1 Takes times to look at objects or people=1
	> 1 yr–3 yrs	19	2.01±0.36 (range: 2.3 to 1.28) (Does not appreciate demoplate=3, not testable=1)	0.05±0.09 (range: 0.00 to 0.3) (Does not appreciate demoplate=2, not testable=3)	Recognizing faces=8 Unable to look or track lights=6 Uses auditory cues mostly=2 Eye contact=5 Eye deviation=1
	> 3 yrs–7 yrs	4	1.84±0.14 (range: 1.98 to 1.7) (not testable=1)	0.1±0.17 (range: 0.00 to 0.3) (not testable=1)	Eye contact=2 Recognizing faces=1 Unable to track objects or people=1 Unable to look or track lights=1 Poor attention=1
PHASE 2 (n = 27)	7m–1 yr	5	1.44±0.25 (range: 1.7 to 1.11)	0.12±0.12 (range: 0.00 to 0.3)	Recognizing faces=3 Eye contact=1 Missing objects on the lower or side field=1 Uses auditory cues mostly=1
	> 1 yr–3 yrs	10	1.51±0.36 (range: 2.13 to 0.98)	0.41±0.23 (range: 0.15 to 0.74) (not testable=1)	Recognizing faces=6 Eye contact=5 Unable to reach out to objects seen=2 Distance viewing tasks=2 Eye deviation=1
	> 3 yrs–7 yrs	12	1.35±0.6 (range: 2.3 to 0.67)	0.31±0.29 (range: 0.0 to 0.9) (Does not appreciate demoplate=1, not testable=1)	Eye contact=6 Unable to reach out to objects seen=2 Recognizing faces=1 Distance viewing tasks=1 Eye deviation=1 Missing objects on the lower or side field=1 Decline in vision after seizure=1 No visual concern=1

(Continued)

Table 2 (Continued).

CVI Range	Age Categories	Number of Children (n = 72)	Grating Acuity (Mean logMAR, Range)	Contrast Sensitivity (Mean logCS, Range)	Visual Concerns (n)*
PHASE 3 (n = 15)	7m–1 yr	1	0.78	0.3	Eye contact=1 Recognizing faces=1
	> 1 yr–3 yrs	2	1.26±0.83 (range: 1.85 to 0.67)	1.06±0.65 (range: 0.6 to 1.52)	Eye deviation=1 Unable to track objects or people=1 No visual concern=1
	> 3 yrs–7 yrs	12	0.59±0.34 (range: 1.13 to 0.19)	1.32±0.46 (range: 0.3 to 1.66)	Missing objects on the lower or side field=4 No visual concern=3 Academic concerns=2 Bumping into objects or people=1 Poor attention=1 Eye deviation=1 Unable to look or track lights=1

Note: *Visual concerns are more in number than the sample, as some parents (n=19) reported more than one visual concern.
Abbreviations: MAR, minimum angle of resolution; CS, contrast sensitivity; m, months; yrs, years.

n = 36) when compared to those in group 2 (mean: 3.41 ± 1.98 years, n = 37) (p = 0.01, Mann–Whitney). Functional vision (p = 0.02, Mann–Whitney) was noted to be significantly poorer in children in group 1 when compared to group 2 (Figure 2 and Table 3).

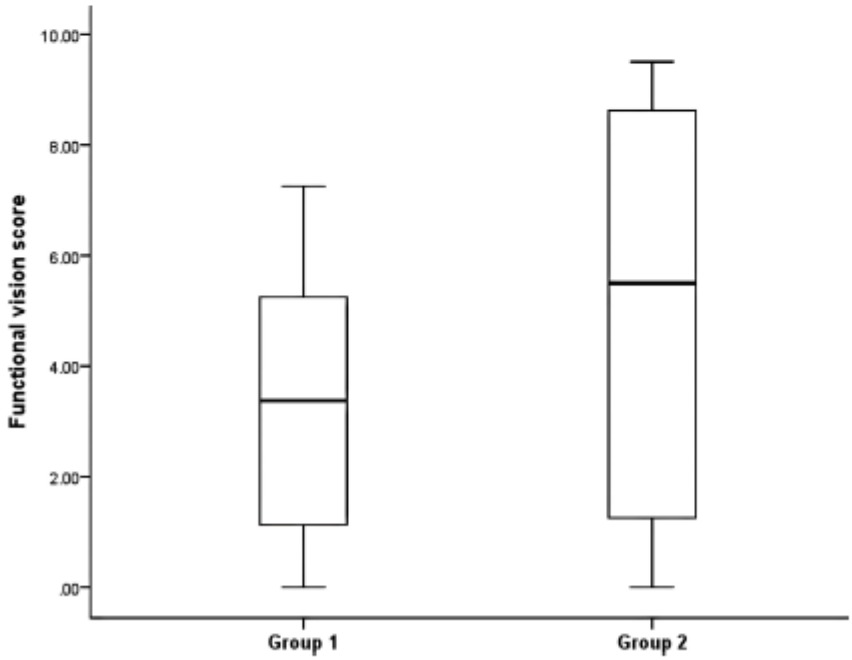

Figure 2 Boxplot representing the functional vision scores in children in group 1 (children reported to have difficulties with face recognition and eye contact) and group 2 (children reported to have other visual concerns) (p=0.02).

Table 3 Comparison of Vision-Related Parameters in Children Reported to Have Difficulty in Face Recognition and Eye Contact (Group 1) and Those Reported to Have Other Visual Concerns (Group 2)

Clinical Parameter	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	p-value
Functional vision score	3.27±2.34 (n=36)	4.97±3.52 (n=36)	0.02
Grating acuity (logMAR)	1.64±0.5 (n=32)	1.31±0.72 (n=33)	0.06
Contrast sensitivity (logCS)	0.18±0.22 (n=28)	0.63±0.64 (n=32)	0.009

Abbreviations: MAR, minimum angle of resolution; CS, contrast sensitivity; SD, standard deviation.

Functional Vision Assessment and Visual Functions

The association between the functional vision score using the CVI Range and visual functions was studied. We were unable to quantify grating acuity and contrast sensitivity in a small proportion of children as they were unable to appreciate the demonstration plate (acuity, n = 5 (6.8%), contrast, n = 4 (5.4%)) despite cooperating for testing. A small percentage of children did not cooperate to complete the test, acuity, n = 2 (2.7%), contrast, n = 8 (10.9%) and functional vision assessment, n = 1 (1.3%) (Table 2).

Chronological ages were significantly different across the 3 phases of CVI (p = 0.001, Kruskal-Wallis), with more younger children (<3 years old) found in phase 1. Grating acuity and contrast sensitivity were also found to be significantly different across the 3 phases of CVI ($p < 0.001$, n = 59) with age as a covariate using linear-mixed model analysis. Grating acuity, contrast sensitivity and chronological age were used in a multiple regression analysis to predict the functional vision score. The prediction model was statistically significant ($F(3, 55) = 63.6$, $p < 0.001$) and accounted for approximately 77% (r^2=0.77) of the variance of functional vision score. The interaction of the three parameters together was found to be the best predictor when compared to an individual or combination of just two parameters. The regression analysis for each predictor variable when other 2 predictors are controlled for is as follows: For every 1.0 logMAR increase (i.e. worsening) in grating acuity, there would be a significant decrease in the functional vision score by 2.8 points ($\beta = -2.8$, $p < 0.001$). However, for every 1.0 logCS increase (ie, better) in contrast sensitivity value, there would be a significant increase in the functional vision score by 1.3 points ($\beta = 1.3$, p = 0.04). However, for every one-month increase in the age, only a small but not significant increase in the functional vision score by 0.02 points was noted ($\beta = 0.02$, p = 0.1).

Visual functions of children whose parents reported difficulty with face recognition and eye contact (considered as group 1) were compared against those whose parents reported other visual concerns (considered as group 2). In case of parents reporting difficulty in face recognition/eye contact along with any other concern, the child was categorized in group 1. Grating acuity was poorer in group 1 when compared to group 2 and was noted to be tending towards significance between both groups (p = 0.06, Mann–Whitney) (Figure 3 and Table 3). Contrast sensitivity was noted to be significantly poorer in children in group 1 when compared to group 2 (p = 0.009, Mann–Whitney) (Figure 4 and Table 3).

Functional Vision Assessment and Chronological Age

Children were divided into 3 categories based on their chronological age (Figure 5). The frequency distribution of all visual concerns (including no visual concerns, n = 5) was found to be comparable across all 3 age categories (p = 0.35, Pearson chi-square). Difficulty in recognizing faces (7 months to 1 year, n = 7, 53.8%; >1 to 3 years, n = 14, 43.8%) and maintaining eye contact (7 months to 1 year, n = 4, 30.8%; >1 to 3 years, n = 10, 31.3%) were noted to be the top two concerns in these age categories. In children above 3 years of age, difficulty in maintaining eye contact remained as a major visual concern (n = 8, 28.6%) followed by missing objects on the lower/side field (n = 5, 17.9%) (Figure 5 and Table 2).

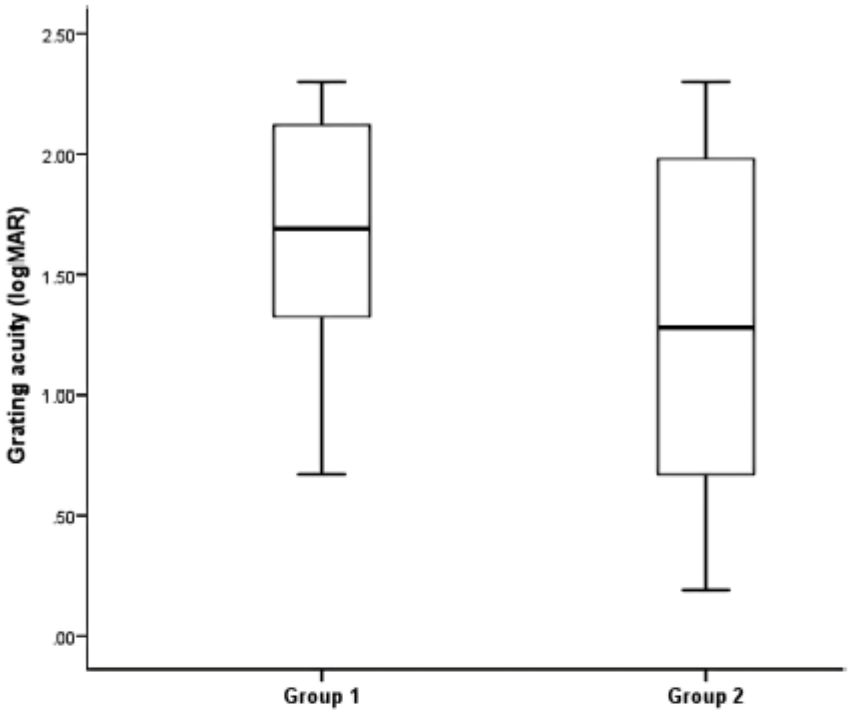

Figure 3 Boxplot representing the grating acuities in children in group 1 (children reported to have difficulties with face recognition and eye contact) and group 2 (children reported to have other visual concerns) (p=0.06).

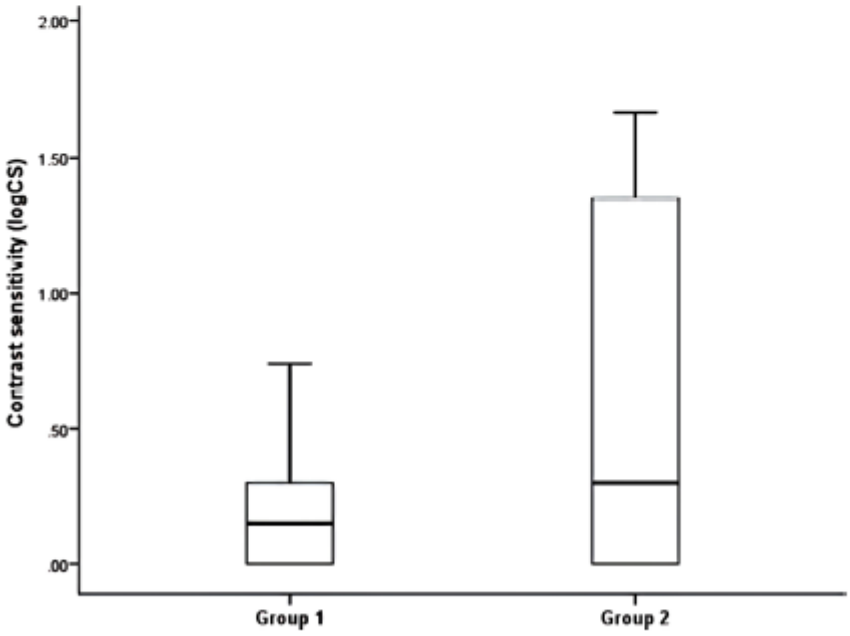

Figure 4 Boxplot representing the contrast sensitivities in children in group 1 (children reported to have difficulties with face recognition and eye contact) and group 2 (children reported to have other visual concerns) (p=0.009).

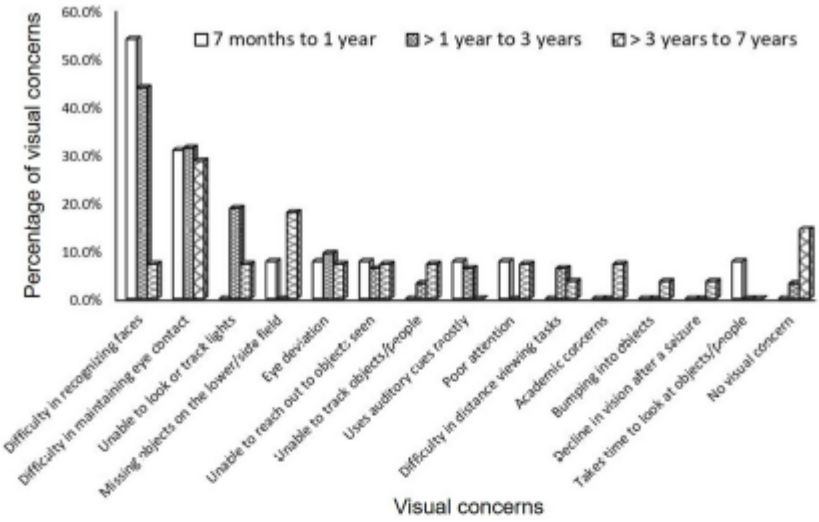

Figure 5 Clustered bar-graph representing the frequency distribution of both visual and no visual concerns based on different chronological age categories (n = 73).
Note: Visual concerns are more in number than the sample, as some parents (n = 19) reported more than one visual concern.

Discussion

This study aimed to document the visual concerns of children with CVI presenting to a pediatric neurology clinic as reported by their parents/caregivers. Fourteen unique visual concerns have been identified in these children with the most common ones being difficulty in maintaining eye contact and recognizing faces. This finding is in agreement with the earlier literature that has reported face identification as one of the symptoms.[20,21]

The significantly different frequency distribution of visual concerns across the 3 phases of CVI based on the functional vision score is an important finding. Functional vision assessment is often carried out in vision rehabilitation centres and is specifically important in children with developmental delays. The functional vision performance in these children could be very different due to interaction of delays in multiple areas (such as vision, fine motor, gross motor, cognition and speech) and may not be fully explained by the ocular diagnosis alone.[22] However, we report that grating acuity, contrast sensitivity and chronological age taken together are able to best predict the functional vision score of the child. These findings indicate the importance of functional vision assessment to understand the child's visual potential that forms the basis to devise suitable vision rehabilitation strategies.[23]

Contrast sensitivity is not as commonly assessed as visual acuity in general clinical examination.[13] In this study, we found that a change in contrast sensitivity measure affects the functional vision score of the child as well. It is therefore important for clinicians to integrate contrast sensitivity testing into their regular clinical practice, interpret the findings and explain contrast enhancing measures to parents as well.[24] An easy-to-remember 3-word strategy for clinicians related to enhancing contrast for children with CVI includes: Big Bold Bright.[24]

Children of parents who did not report any vision concern (phase 3 = 4, phase 2 = 1) had a range of acuity between 0.19 (close to normal) and 1.28 logMAR (moderate visual impairment) and contrast sensitivity ranging from 0.6 (reduced) to 1.66 (normal/near normal) logCS. This indicates that parents may not always be able to identify visual concerns in children with CVI even if their acuity and contrast are significantly reduced. Developmental delays could make it harder for parents to notice visual problems. Our study findings highlight that parents of all children with CVI should be questioned about the child's functional vision problems as in some children these problems can be missed or not looked for. Upon questioning, parents will also be aware to look for those domains of functional vision. Children with poor eye contact, inability to recognize faces or look at or track lights were easily identified by the parents as having difficulties with visual problems and this was co-related with clinical measures of visual function.

As mentioned previously, pediatric ophthalmology/optometry services largely remain referral-based services for children with neurological visual impairment, eg, CVI. This is most likely due to the child having multiple developmental delays and motor and speech being the more obvious areas compared to vision. This is also reflected in the very low percentage of children (15%) in our study who previously had an ophthalmology/optometry assessment. Educating parents/caregivers about ocular conditions in children that need evaluation is useful and is the key to plan better rehabilitation strategies and provide guidance to therapists. A recent study highlighted the lack of awareness of early detection of CVI amidst clinicians and emphasized the need for more research from different geographic areas, ethnicities, etc.[21] The results of our study contribute towards this effort to expand this literature base.

As the assessment and management of children with CVI is multi-disciplinary,[25] it requires close collaborative work between professionals and need-based cross referrals. In one of our ongoing studies, we have found a moderate correlation between the developmental quotient and the functional vision score ($r = 0.5$).[26] This highlights the importance of referral by the developmental psychologist/pediatrician in referring children with lower developmental quotients for comprehensive eye care services and for eye care professionals to refer for an assessment of the child's overall development if the child is noted to have poor functional vision. Early intervention therapists primarily physiotherapists, occupational therapists, speech therapists and special educators regularly interact with children having developmental delays with underlying causes of neurological conditions such as cerebral palsy as part of their therapy sessions. Approximately 60–70% of children with cerebral palsy also have CVI.[27,28] Therefore, it is important to raise awareness among these professionals as well about the vision concerns that these children are likely to exhibit.

The current study has few limitations. As CVI remains a diagnosis of exclusion, a firm diagnostic criteria have always been elusive. In our study, the diagnosis of CVI was made by the pediatric neurologist based on the MRI findings, medical history and general observation of visual behaviour. Comprehensive eye evaluation findings were only available in a small proportion of children (28.7%), among whom optic atrophy was noted to be high (66.6%), similar to other studies.[29,30]

In the current study, we used "within-the-characteristic" rating scale for assessing functional vision. Roman-Lantzy reports that the scores of the two rating scales can be similar but generally not identical.[12] In a separate study carried out by our rehabilitation professionals, "across-the-characteristic" rating scale took approximately 40 minutes to 1 hour (unpublished results). Therefore, considering the time constraints, "within-the-characteristic" rating scale was used as a surrogate measure to categorize the children based on their functional vision. However, the authors agree that it would have been ideal to use both the rating scales and arrive at a final functional vision score. It is important to note that the scores obtained in this study were not used to plan rehabilitative strategies for children. Instead, all children who were recruited in the study were recommended a comprehensive rehabilitative assessment along with an eye examination. These results have not been discussed here, as they are beyond the scope of this paper.

The vision-related parameters of children with concerns of difficulty in face recognition and eye contact were significantly poorer (contrast sensitivity, $p = 0.009$ and functional vision, $p = 0.02$; grating acuity was tending towards significance, $p = 0.06$) when compared to those with other visual concerns; however, they were also significantly younger ($p = 0.01$). These findings indicate that these two visual concerns (i.e. face recognition and eye contact) are important to be asked to the parents/caregivers to help decide referral in addition to other referral parameters used by pediatric neurologists for children with CVI to undertake comprehensive eye evaluation, particularly in younger children in whom the parents may not have noticed any obvious visual limitation. Identifying these visual concerns early help in early diagnosis and referral. However, the current study has not looked into the specificity of these questions and it should be noted that children with other special educational needs, such as autism spectrum disorder, can also have concerns with eye contact.

Detailed structured questionnaires have been developed for children with CVI.[31–33] These are primarily used in pediatric ophthalmology and vision rehabilitation centres and may be difficult to use in neurology clinics owing to time constraints. The most commonly reported concerns in this study included difficulty in recognizing faces and maintaining eye contact. These 2 concerns along with bumping into objects and eye deviation were also noted as the primary reasons by parents visiting a special needs vision clinic in a heterogeneous group of children with special needs.[34] It would be useful to add these concerns as a part of the brief vision history that can be elicited in pediatric neurology clinics.

Additionally, observing whether the child can fixate and follow light can form part of a quick assessment, as this was also reported to be the third most common concern in our study.

Conclusion

A basic vision-related history and quick assessment in the pediatric neurology clinic can result in early referrals to eye care and vision rehabilitation services. Particularly, children having a poor functional vision score may also have an associated reduction in grating acuity and contrast sensitivity. Appropriate refractive correction can improve the vision in these children to a certain extent, which could then have an associated improvement in the functional vision score and thereby positively impact the overall development of the child. This, however, needs further research.[35]

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Disclosure

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

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A16. Scientific poster-I presented in the Association for Research in Vision and Ophthalmology (ARVO), May 2022

DOES VISION CORRELATE WITH OVERALL DEVELOPMENT IN CHILDREN WITH CEREBRAL VISUAL IMPAIRMENT?

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INTRODUCTION

- Visual learning contributes significantly to overall development in early childhood.[1]
- Children with neurological conditions such as cerebral visual impairment (CVI) are likely to have delays/disabilities in one or more developmental areas such as in speech, motor and cognition. [2]
- Visual concerns particularly in pre/non-verbal children can go unnoticed compared to more obvious motor or speech delays.

PURPOSE

To determine the correlation between vision-related parameters and the overall development of children with CVI.

METHODS

- Prospective, cross-sectional study carried out in a tertiary pediatric neurology clinic, in Hyderabad, India

Age: 6 months to 7 years with cerebral visual impairment

DDST-II: Denver Developmental Screening Test-II
TAC II:Teller acuity cards II
OCC: Ohio contrast cards

Ethics approval was obtained from affiliated institutions. Parents gave written informed consent.

- Assessment of developmental quotient using DDST-II
- Functional visual assessment using CVI range and categorized into 3 phases
- Grating acuity (using TAC II) and contrast sensitivity (using OCC) assessment

Figure 1 Flow chart demonstrating the study protocol

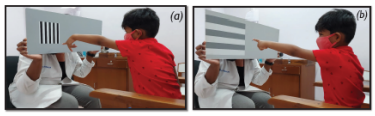


Figure 2 :Assessment using Teller acuity cards II (a) and Ohio contrast cards (b)
*(*informed consent obtained for photographs)*

- The domains assessed using DDST-II include: gross motor, fine motor-adaptive, personal-social and language.

Characteristics in CVI range	
Color preference	Light-gazing and non-purposeful gaze
Need for movement	Difficulty with distance viewing
Visual field preference	Atypical visual reflexes
Visual latency	Difficulty with visual novelty
Difficulty with visual complexity	Absence of visually guided reach

Table 1:Ten visual characteristics noted in children with cerebral visual impairment

- Linear mixed model analysis adjusting for age was carried out using SPSS (version 20).

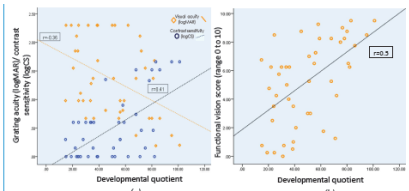
RESULTS

Characteristics	CVI (n=47)
Age (mean±SD) (years) Range	2.9±1.74 9 months to 6.83 years
Gender Males (n,%) Females (n,%)	 35 (74.4%) 12 (25.6%)
Binocular grating acuity (logMAR) Mean±SD Range	 1.35±0.67 2.27 to 0.37
Binocular contrast sensitivity logCS) Mean±SD Range	 0.49±0.56 0.0 to 1.66

Table 2 Demographic and clinical characteristics of children with cerebral visual impairment (n=47)

Grading of CVI (functional vision)	Age (mean ±SD) (years)	Grating acuity (mean logMAR±SD)	Contrast sensitivity (mean logCS±SD)	Developmental quotients (mean DQ±SD)
Phase I (n=13)	1.66±0.65	2.24±0.11	0.0±0.0	38.29±16.82
Phase II (n=19)	2.63±1.51	1.26±0.41	0.35±0.26	42.27±20.78
Phase III (n=15)	4.4±1.93	0.75±0.37	1.07±0.57	69.4±19.98

Table 3: Distribution of children in three phases of CVI (significant differences in grating acuity across three phases of cerebral visual impairment, p<0.01; contrast sensitivity and developmental quotients are significantly different in phase 3 compared to the other 2 phases, p<0.01) (using linear mixed model analysis-age adjusted)



logMAR, p=0.01, R^2=0.2; logCS, p<0.01, R^2=0.3; functional vision score, p=0.02, R^2=0.3

Figure 3 :Scatter plots demonstrating correlation between developmental quotients and visual functions (a) and functional vision score (b)

CONCLUSIONS

- Vision parameters correlate with developmental quotient in children with CVI (Table 3 & Figure 3).
- Results do not establish any causation between the two parameters (vision parameters vs. developmental quotient).
- Children with lower developmental quotients could have poorer visual functions due to challenges in eliciting appropriate responses due to poor visual attention and cognition.

TAKE HOME MESSAGE

- ❑ Children with poor visual functions need to be assessed for their overall development by developmental pediatrician/psychologist.
- ❑ Children with lower developmental quotients should be referred to pediatric eye care specialist.
- ❑ Such cross referrals will help in identifying need-based early intervention therapies.

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A17. Scientific poster-II presented in the Association for Research in Vision and Ophthalmology (ARVO), May 2022

REPEATABILITY OF GRATING ACUITY AND CONTRAST SENSITIVITY TESTS IN CHILDREN WITH CEREBRAL VISUAL IMPAIRMENT

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[5] Pediatric Neurology and Rehabilitation, Rainbow Children's Hospitals, Hyderabad, India

INTRODUCTION

- Children with neurological conditions such as cerebral visual impairment (CVI) are likely to have delays/disabilities in one or more developmental areas such as in speech, motor and cognition.[1]
- Location/extent of brain damage, frequency of seizures and medication can contribute to the variability of clinical measurements in these children.[2]
- It is important to identify clinical tools with good repeatability to monitor the effectiveness of any intervention.

PURPOSE

To determine the repeatability indices of grating acuity [Teller acuity cards (TAC), Peekaboo Vision app (PV)] and contrast sensitivity [Hiding Heidi cards (HH) and Ohio contrast cards (OCC)] tests in children with CVI.

METHODS

- Prospective, cross-sectional study was carried out in a tertiary pediatric neurology clinic in Hyderabad, India. Ethics approval was obtained from all the affiliated institutions. Parents gave written informed consent.
- Study participants: Children with CVI (6 months to 7 years of age).
- Retest was carried out after an average duration of 3.5 months.

Figure 1: Assessment of grating acuity using Peekaboo Vision app (a),Teller acuity cards II (b); contrast sensitivity using Hiding Heidi (c) and Ohio contrast cards (d)
**Informed consent obtained for photographs*

RESULTS

Characteristics	CVI (n=32)
Age (mean±SD)	2.61±1.72 years
Range	9 months to 6.83 years
Gender	
Males (n,%)	22 (68.8%)
Females (n,%)	10 (31.2%)

Table 1: Demographic characteristics of study participants (n=32)

Test	Testing time (mins) (Mean±SD)	p-value
Grating acuity		
Teller acuity cards II	2.28±1.21	0.76
Peekaboo Vision app	2.29±0.91	
Contrast Sensitivity		
Hiding Heidi	1.13±0.52	<0.01
Ohio contrast cards	1.24±0.68	

Table 2: Testing time comparisons between the two grating acuity and contrast sensitivity tests

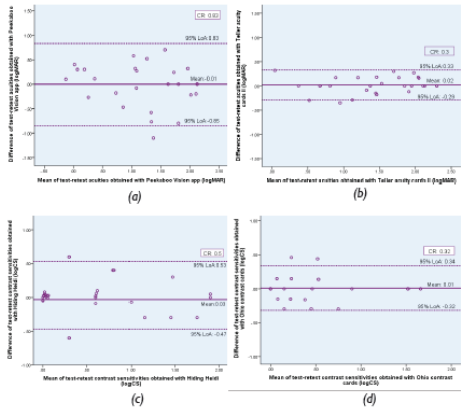

Figure 2: Bland-Altman plots of agreement between test-retest measures of tests of grating acuities: Peekaboo Vision app (a), Teller acuity cards II (b) and contrast sensitivities: Hiding Heidi (c), Ohio contrast cards (d). CR= coefficient of repeatability.
Note:The offset jitter of some data points is done purely for visualization purposes

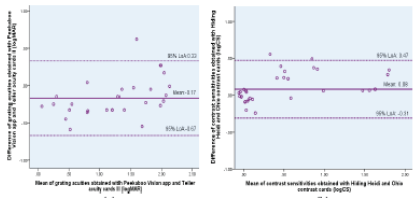

Figure 3a: Bland-Altman plots of agreement between Peekaboo Vision app and Teller acuity cards II

Figure 3b: Bland-Altman plots of agreement between Hiding Heidi and Ohio contrast cards

Note:The offset jitter of some data points is done purely for visualization purposes

CONCLUSIONS

- Repeatability (Figure 2) was found to be better for TAC II and OCC in measuring grating acuity and contrast sensitivity respectively.
- Better grating acuity was documented with Peekaboo Vision app and better log contrast sensitivity was measured with Hiding Heidi (Figure 3).
- Differences between the tests could be due to different testing techniques, thresholding paradigms, different step sizes measured and different types of stimuli shown.
- Different tests may not be used interchangeably. The choice of tests of visual functions for children with CVI should consider the repeatability measure, especially for longitudinal follow-ups.

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A18: Conference presentations, awards and recognitions

Conference presentations

1. Parent-reported visual concerns in children with cerebral visual impairment presenting to a pediatric neurology clinic, Indian Eye Research Group, ARVO-India chapter, July 2023, Madurai, India- Scientific Poster
2. Clinical utility of 'Peekaboo Vision' application in children with Down syndrome, Vision 2022- The 13th International Conference on Low Vision Research and Rehabilitation (ISLRR-2022), July 2022, Dublin – Scientific paper
3. Vision assessment of children with cerebral visual impairment – ResMeet 2022, organized by India Vision Institute, June 2022 (virtual) – Scientific paper
4. Does vision correlate with overall development in children with cerebral visual impairment?, Association for Research in Vision and Ophthalmology-2022 (ARVO-2022) – Scientific poster
5. Repeatability of grating acuity and contrast sensitivity in children with cerebral visual impairment, Association for Research in Vision and Ophthalmology-2022 (ARVO-2022) – Scientific poster (co-author)
6. Does vision correlate with overall development in children with cerebral visual impairment? Association of Child Neurology (ChildNeurocon), Feb 2022 (virtual)– Scientific poster
7. Validation of clinical tools to measure visual functions in children with cerebral visual impairment. Annual symposium of City, University of London, London, UK and L V Prasad Eye Institute, Hyderabad, India, Jan 2022 (virtual) – Scientific paper
8. How repeatable are tests of visual functions in children with cerebral visual impairment? 8th School of Health Sciences Annual Doctoral Research Conference – November 2021(virtual) - Scientific paper
9. Contrast sensitivity in children with cerebral visual impairment, Annual meeting of American Academy of Optometry – November 2021 (virtual) - Scientific paper
10. How does vision correlate with overall development in children with cerebral visual impairment? Indian Eye Research Group, ARVO-India chapter (virtual) - October 2021 – Scientific paper
11. Children with cerebral visual impairment: how well do we understand their visual world? British Congress of Optometry and Vision Sciences conference (virtual) - September 2021 – Highlighted early career researcher talk

12. Validation of tests of visual functions in children with cerebral visual impairment, Annual symposium of City, University of London, London, UK and L V Prasad Eye Institute, Hyderabad, India, Jan 2021- (virtual)– Scientific paper
13. Parents reported visual concerns in a population of children with special needs in India in British Congress of Optometry and Vision Sciences- September 2020 (virtual) – Scientific poster

Awards and recognitions

1. Envision-Atwell's honourable mention and cash award, Low vision research group, The Association for Research in Vision and Ophthalmology conference (ARVO)-2022, Denver, USA
2. People's choice award winner, Global Young Scientists Summit (GYSS)-2022, Singapore (virtual)
3. Nominated and selected to participate in GYSS-2022, Singapore (virtual)
4. Developing Country Eye Researcher Fellowship, ARVO-2022, Denver, USA
5. Highlighted early career researcher, British Congress of Optometry and Vision Sciences conference-2021 (virtual)
6. 1st runner-up, 3-minute thesis competition university finals held by City, University of London, London, UK in 2021 (virtual)
7. Travel fellowship awardee, Vision 2022 – The 13th International Conference on Low Vision Research & Rehabilitation, Dublin