Visual function subtyping in children with early-onset cerebral visual impairment

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This article is commented on by Dutton on page 245 of this issue.

PUBLICATION DATA
Accepted for publication 18th August 2020.
Published online

ABBREVIATIONS

Beery-VMI	Beery Buktenica Test of Visuo-Motor Integration
CVI	Cerebral visual impairment
MDS	Multidimensional scaling
TVPS-3	Test of Visual Perceptual Skills, Third Edition
VCI	Verbal Comprehension Index

AIM To develop a data-driven subgrouping method to identify and profile subtypes of early-onset childhood cerebral visual impairment (CVI).
METHOD Sixty-three children with suspected or diagnosed congenital CVI were recruited (28 males, 35 females, median age=8y, range=5–16y). Cognitive, basic, and higher-order vision functions were assessed and quality of life, functional vision questionnaire, neurodevelopmental, and ophthalmological data were collected. Cluster analysis and other statistical analyses were undertaken to determine and validate the subgrouping.
RESULTS Forty-three participants completing the full test battery were included in cluster analysis, revealing two subgroups. Group A1 (n=15) showed selective visual perception and visuomotor deficits. Group A2 (n=28) showed more severe and broader visual perception and visuomotor deficits, and variable visual acuity. A third, lower-functioning group, Group B (n=20), was differentiated and showed significant visual acuity reduction compared with Group A (p<0.001, V=0.69). External validation showed significant cooccurring ophthalmological (e.g. strabismus p<0.001, V=0.59) and motor impairment differences (χ^2=16.26, p<0.001, V=0.51) between the three groups. All groups had lowered parent-reported quality of life and everyday functional vision.
INTERPRETATION Statistical analyses revealed three subgroups with differentiated vision function characteristics on a gradient of severity. The subgrouping method provides the first steps in developing a novel classification system to underpin future clinical diagnostics and profiling of early-onset CVI.

Cerebral visual impairment (CVI) is a complex disorder associated with heterogeneous visual dysfunctions arising from brain injury or abnormality.[1,2] It is the most common cause of childhood visual impairment in high-income countries.[3,4] The economic, social, and personal burden of CVI is high, with adverse effects of coexisting disorders increasing the burden further.[5]

Despite these needs, there is lack of consensus on the definition, assessment, and diagnostic methods to identify CVI,[6] and limited knowledge of whether it is a unitary condition or composed of discrete subtypes. The spectrum of vision function characteristics ranges from severe to mild or near-typical visual acuity reduction and diverse higher-order visual perceptual difficulties, commonly coexisting with other neurodevelopmental impairments.[1,7,8] This study takes a broad operational definition of CVI as 'a *verifiable* visual dysfunction, which cannot be attributed to disorders of the anterior visual pathways or any potentially cooccurring ocular impairment',[6] as in other European centres.[9] As this was an exploratory study, it set out to investigate the wide range of possible visual dysfunctions ranging from normal visual acuity to severe visual acuity or field loss, as indicated by the literature.

Towards greater clarity of this complex phenomenon, there have been calls to investigate whether CVI falls into identifiable subgroups warranting systematic classification.[2] Previous classification attempts have been limited to descriptive accounts with face validity only.[1,8] Systematic reviews of the literature have therefore proposed that future classification should be empirical, data-driven, and based on quantifiable assessment of commonly associated visual dysfunctions.[2,6]

Therefore, this study set out to determine and subgroup visual dysfunctions through the use of a battery of standardized clinical tests. It was anticipated that some children would not be able to undertake the full battery of assessments because of severity of vision, cognitive, and motor constraints, and that the study would provide insights into the possible full spectrum of function and severity. Data-driven cluster analysis would be undertaken with those able to undertake the full battery of testing to establish any potential subgroups, followed by statistical validation with multidimensional scaling (MDS). As higher-order vision dysfunctions (or 'higher vision') would be measured through visual perception standard tests, which are developmentally normative, test scores would be

 DOI: 10.1111/dmcn.14710

compared with age norms and verbal cognition to differentiate from general cognitive status. The research questions were: (1) do children with suspected or clinically diagnosed CVI cluster into subgroups according to vision functions and, if so, what are the profiles of these groups, and (2) do the subgroups differ according to 'external variables', such as aetiological risk factors, cooccurring neurodevelopmental impairments, parent-reported quality of life, or everyday vision? This study aimed to identify subgroups that could underpin a future classification system of CVI to support clinical diagnostics.

What this paper adds

- Three data-driven subgroups of vision function deficits were identified.
- A similar severity gradient was shown in cooccurring cognitive and neurodevelopmental deficits.
- Reported quality of life and functional vision difficulties were low across all groups.

METHOD

Definitions

Diagnosis/suspicion of CVI

Children with all levels of visual ability, as measured by visual acuity, were included in this study in line with the European consensus and definition of CVI.[9] As no consensual national guidelines exist for the clinical assessment of CVI and the medical diagnosis of the condition is not reliably standardized across clinical services,[2] not all children with the condition may actually receive a diagnosis.[1,10,11] Children with concerns regarding complex higher-order visual difficulties are not necessarily referred to specialist ophthalmological or neurodisability clinics.[10,11] To include this wider range, children with a suspected CVI condition, as well as those with a confirmed clinical diagnosis, were invited to participate. For the children with suspected CVI, parents needed to report significant difficulties in everyday life that appeared to be associated with functional vision.[11] All parents were interviewed before inclusion to establish whether problems reported appeared to be vision-based. All children underwent clinical examination by an ophthalmologist (RB) and orthoptist (RK) (see 'Ophthalmological data' for further details). Only those children whose visual difficulties were likely to be caused primarily by brain disorders were included in the final study sample, and those judged to be caused primarily by congenital disorders of the peripheral visual system[12] were excluded.

Neurodisability paediatrician assessment

For very low-functioning children with cooccurring conditions (e.g. intellectual disability or cerebral palsy [CP]), a neurodisability paediatrician (JS) was consulted about whether the child's behavioural symptoms were likely to be indicative of a visual difficulty. All children had a known history of a pre- or perinatal event that is associated with brain injury and abnormality, or had cooccurring conditions indicative of brain abnormality. After assessment, only children whose symptoms of concern were considered likely to be of visual origin were included.

Participants

No power analyses to determine sample size were possible a priori as this study had not been undertaken previously, but a sample of n=70 was planned to enable multivariate analyses with up to seven input variables planned for cluster analysis.[13]

Convenience sampling recruitment was conducted through two national paediatric/eye hospitals and parent self-referral. Inclusion criteria were: (1) age 5 to 15 years and (2) suspected or diagnosed congenital CVI (see 'Definitions'). Although diagnosis could be external to the study site, the ophthalmologist (RB) confirmed that the visual problems were not primarily caused by disorders of the anterior visual pathways (globe, retina, or anterior optic nerve). In addition, children who were lower functioning were examined by the neurodisability paediatrician (JS) before a decision was made regarding inclusion (see 'Definitions').

Exclusion criteria were: (1) acquired CVI (onset >4wks after birth), (2) visual difficulties primarily caused by disorders of the anterior visual pathways (globe, retina, or anterior optic nerve disorder), and (3) insufficient parental understanding of English to complete study questionnaires.

As part of the inclusion sampling, a subsample of 26 children with vision better than logMAR 1.0 and estimated development in line with age expectations was sought to permit more detailed exploratory neuropsychological testing (not reported here).

Design and procedure

A cross-sectional observational study was conducted at the hospital research site (between 2014 and 2017). Information about the child's paediatric history and any related diagnoses were obtained through medical case-note review and parent reporting. Participants attended a single research assessment where cognition, vision, and other tests were administered by the neuropsychology researcher (HS), who was trained and supervised to administer the tests by the neuropsychologist (ND), paediatrician, ophthalmologist, and orthoptist of the study group. Participants were tested with both eyes open with best corrected vision (i.e. vision using the correct prescription). Each child also had a routine clinical ophthalmology examination (RB and RK) and the medical case notes were accessed.

Measures

Standardized age-appropriate tests with available paediatric normative data were selected to assess visual functions identified as being relevant to CVI in the literature.[1,14] Other exploratory non-standardized vision and specialized neuropsychological tests included in the study are not reported here.

Vision testing materials

Visual acuity. Participants able to match optotypes completed the Sonksen LogMAR test at 40cm standard distance (near acuity).[15] Those unable to perform matching

Table 1: Sample vision characteristics (n=63)

Vision domain	Test	Number who undertook test, n (%)	Test scores, n (% of total number undertaking test)
VA	Sonksen LogMAR ranges (recognition acuity)	50 (79)	Normal VA (0.00–0.20): 29 (46)
	Keeler cards (resolution acuity)	11 (17)	Near normal VA (0.21–0.30): 5 (8)
	Near Detection Scale/clinician estimate (detection acuity)	2 (3)	Socially significant VI (0.31–0.49): 6 (10)
			Moderate VI (0.50–1.00): 16 (25)
			Severe VI (1.01–1.30): 4 (6)
			Blind (<1.30): 3 (5)
Visual fields	Confrontation	25 (40)	Normal: 24 (53)
	SVOP perimeter	4 (6)	Right-field defect: 9 (20)
	Octopus perimeter	8 (13)	Left-field defect: 3 (7)
	Other measure	8 (13)	Inferior field defect: 4 (9)
	Missing	18 (29)	Generalized field loss: 5 (11)
CS	Hiding Heidi	61 (97)	Hiding Heidi:
	LEA Symbols Low Contrast	51 (81)	Normal: 50 (82)
			Lowered: 11 (18)
			Optotypes:
			Normal: 37 (73)
			Lowered: 14 (27)
Stereopsis	Frisby Stereotest	48 (76)	Good quality (≤40s arc): 12 (25)
			Mid-quality (41–300s arc): 6 (13)
			Weak quality (≥300s arc): 7 (15)
			Absent: 23 (48)
			Test scores, mean (SD)
Visual perception	TVPS-3 total	43 (68)	79.88 (18.78)
Visuomotor integration	Beery-VMI	43 (68)	73.77 (13.93)
Use of vision in daily life	CVI Inventory	61 (97)	56.09 (12.88)
Quality of life (PedsQL)	Psychosocial	61 (97)	40.62 (14.47)
	Physical		37.80 (22.97)
	Total		39.68 (15.42)

VA, visual acuity; logMAR, logarithm of the minimal angle of resolution; VI, visual impairment; SVOP, saccadic vector optokinetic perimetry; CS, contrast sensitivity; TVPS-3, Test of Visual Perceptual Skills, Third Edition; Beery-VMI, Beery Buktenica Test of Visuo-Motor Integration; CVI, cerebral visual impairment; PedsQL, Pediatric Quality of Life Inventory.

tasks completed resolution acuity tests with Keeler Acuity Cards at 38cm standard distance.[16] For children who could not produce reliable responses to either type of test, but for whom objective evidence of vision sufficient to support recognition of basic visual targets was available, a broad estimate of acuity level was made (Near Detection Scale[17] n=1, JS clinician estimate n=1). Visual acuity scores were categorized according to the World Health Organization, as adapted by Cumberland et al.,[18] using the most detailed acuity score obtained for each child (see definitions of logMAR ranges in Table 1).

Contrast sensitivity. The Hiding Heidi low-contrast face test was administered (http://www.lea-test.fi). Those able to match symbols completed the LEA Symbols Low Contrast test (http://www.lea-test.fi). Both tasks were administered as reported by Leat and Wegman;[19] the category of 'normal' performance was the ability to identify all targets at 1.25% contrast.

Stereoacuity. The Frisby Stereotest was administered to assess three-dimensional vision; scores were coded into ordinal categories according to the manual.[20]

'Higher vision'. The Test of Visual Perceptual Skills, Third Edition (TVPS-3) was administered and scored according to the manual.[21] The total score and seven subtests (Tables 2 and S1, online supporting information) were investigated.

The Beery Buktenica Test of Visuo-Motor Integration (Beery-VMI) and supplementary tasks of motor-free visual perception and motor coordination were administered and scored according to the manual.[22]

Standard scores for TVPS-3 total score, Beery-VMI, and supplementary tasks of motor-free visual perception and motor coordination have a mean of 100 (SD=15). Scaled scores for TVPS-3 subtests have a mean of 10 (SD=3). Standard scores less than 80 and scaled scores less than 6 were rated in the 'clinically impaired' range.

External variables

Cognition. The Verbal Comprehension Index (VCI) of the Wechsler Intelligence Scales for Children, Fourth Edition[23] was administered to participants aged 6 years and above, and the VCI of the Wechsler Preschool and Primary Scales of Intelligence, Fourth Edition[24] to those under 6 years of age. The sensorimotor understanding subscale of the Reynell Zinkin Scales[25] was administered to children below the developmental age of 5 years. Standard administration and scoring were undertaken with one modification on one Wechsler Intelligence Scales for Children, Fourth Edition comprehension vision-related item, in line with Bathelt et al.[26] The Reynell Zinkin Scales were scored according to sighted age-equivalent norms and a developmental quotient was calculated according to Dale and Sonksen.[27] VCIs and developmental quotients were considered as IQ estimates for standard categorization across the sample.[28]

Functional questionnaires. The parent-report Pediatric Quality of Life Inventory (4.0 UK) was used to investigate

Table 2: Vision characteristics of the three classification subgroups (shortened version; for full version see Table S1, online supporting information)

Domain	Test/grading scale	Group A1 (n=15)	Group A2 (n=28)	Group B (n=20)	Group A1 and A2 comparison (95% CI)	Group A1, A2, and B comparison
Visual acuity	Cumberland et al.[18] category					p<0.001, V=0.69, A1>A2>B[b]
	Normal	15 (100%)	14 (50%)	0		
	Near normal	0	4 (14%)	1 (5%)		
	Socially significant VI	0	3 (11%)	3 (15%)		
	Moderate VI	0	7 (25%)	9 (45%)		
	Severe VI	0	0	4 (20%)		
	Blind	0	0	3 (15%)		
	Sonksen logMAR, median (IQR)	0.00 (0.00–0.03)	0.21 (0.10–0.46)		U=48.5, p<0.001, η^2=0.42, A1>A2[b]	
CS	Hiding Heidi category					
	Normal	15 (100%)	26 (93%)	9 (50%)[a]		p<0.001, V=0.54, A1>A2>B[b]
	Lowered	0	2 (7%)	9 (50%)[a]		
	Missing			2		
	LEA Symbols Low Contrast, mode (range)	30 (28–30)	30 (10–30)		U=176.0, p>0.05	
Stereopsis	Frisby Stereotest category					
	Good quality	12 (80%)	0		U=4.5, p<0.001, η^2=0.79, A1>A2[b]	
	Mid-quality	3 (20%)	3 (11%)			
	Weak quality	0	5 (18%)			
	Absent	0	20 (71%)			
Visual fields	Normal	10 (71%)[a]	12 (52%)[a]	2 (25%)[a]		
	Right defect	2 (14%)[a]	5 (22%)[a]	2 (25%)[a]		
	Left defect	1 (7%)[a]	2 (9%)[a]	0		
	Inferior field loss	0	1 (4%)[a]	3 (38%)[a]		
	Generalized field loss	1 (7%)[a]	3 (13%)[a]	1 (13%)[a]		
	Missing	1	5	12		
Visual perception	TVPS-3 total, mean (SD)	88.93 (19.30)	75.04 (16.91)			
	Normative comparison (95% CI)	t(14)=−2.22, p=0.043 (−21.75 to −0.38)	t(27)=−7.81, p<0.001 (−31.52 to −18.41)		t(41)=2.45 p=0.019 (2.42–25.37) A1>A2[b]	
	VCI comparison (95% CI)	t(14)=−1.71, p>0.05 (−2.33 to 20.73)	t(27)=3.99, p<0.001 (6.82–21.25)			
Visuomotor integration	Beery-VMI, mean (SD)	79.33 (10.97)	70.79 (14.60)			
	Normative comparison (95% CI)	t(14)=−7.30, p<0.001 (−26.74 to −14.59)	t(27)=−10.59, p<0.001 (−34.87 to −23.55)		t(41)=1.98, p>0.05 (−0.16 to 17.25)	
	VCI comparison (95% CI)	t(14)=4.03, p=0.001 (8.79–28.81)	t(27)=5.61, p<0.001 (11.60–24.97)			
CVI Inventory, mean (SD)		53.18 (17.62)	55.43 (11.88)	59.73 (8.90)		F(2, 57)=1.11, p>0.05, η^2=0.042
	Missing			2		
PedsQL	Total, mean (SD)	38.70 (16.38)	42.19 (15.68)	36.59 (14.35)		F(2, 58)=0.76, p>0.05 η^2=0.02
	Normative comparison (95% CI)	t(14)=−10.03, p<0.001 (−51.50 to −33.35)	t(27)=−13.14, p<0.001 (−45.02 to −32.85)	t(17)=−13.17, p<0.001 (−51.66 to −37.39)		
	Missing			2		

[a]For variables with missing data points, the percentage is calculated from the total valid responses. [b]For statistically significant between-group differences, the trend direction is reported. CI, confidence interval; V, Cramer's V effect size; VI, visual impairment; logMAR, logarithm of the minimal angle of resolution; IQR, interquartile range; η^2, eta squared effect size; U, Mann–Whitney U test; CS, contrast sensitivity; TVPS-3, Test of Visual Perceptual Skills, Third Edition; VCI, Verbal Comprehension Index; Beery-VMI, Beery Buktenica Test of Visuo-Motor Integration; Beery-VP, Beery-VMI supplementary task of motor-free visual perception; Beery-MC, Beery-VMI supplementary task of motor coordination; CVI, cerebral visual impairment; PedsQL, Pediatric Quality of Life Inventory.

paediatric health-related quality of life with published UK norms.[29] The CVI Inventory, a 51-item validated parent-report questionnaire, measured vision-related everyday behaviours;[30,31] total scores were standardized to account for variation in valid responses, with scores ranging from 0 (all items scored 'never difficult') to 100 (all applicable items scored 'always difficult'; see Appendix S1, online supporting information).

Ophthalmological data. Routine clinical examination conducted by RB and RK included fundoscopy, retinoscopy, ocular motility, corneal reflexes, convergence, and visual field assessment (Tables 2 and S1). For further scrutiny of the original clinical diagnosis of CVI, RB also determined whether each child's CVI diagnosis could be clinically confirmed by assessment of the ophthalmologist. Two of the following three criteria needed to be fulfilled: (1) known history of a pre- or perinatal event that is associated with brain injury and abnormality (clear histories of causative events), or cooccurring conditions indicative of brain abnormality (such as movement disorder); (2) convincing symptoms of functional vision difficulties in daily life reported by parents; and (3) objective evidence of visual difficulties on examination (RB did not have access to the research test results).

Statistical analysis

Analyses were undertaken using SPSS v25 (IBM Corp., Armonk, NY, USA). It was anticipated a priori that not all children would be able to undertake all of the vision tests because of both visual and cognitive demands. The statistical methods were planned to encompass either the full sample or the subsample(s) who had sufficient vision and cognitive abilities to undertake the full assessment battery. The subsample unable to complete the full assessment because of visual acuity worse than 1.0 logMAR and/or developmental quotient less than 5 years was identified and separated from those who completed the full battery (missing data are reported in Tables 1–3).

For those children completing the full battery of tests (n=43), a principal components analysis was undertaken with the main variables selected for the classification analysis. These variables were Sonksen LogMAR, LEA Symbols Low Contrast test, and Frisby Stereotest raw scores, and TVPS-3 total and Beery-VMI standard scores (all variables rescaled onto a 0–1 scale to permit comparison across different computation notations). After selection of these five input variables, a priori hierarchical agglomerative cluster analysis was conducted using Ward's linkage and squared Euclidean distance. Cluster analysis is a set of heuristic methods used to classify cases into groups based on statistical similarity.[13] The optimal cluster number was determined by the distances between each clustering stage (see Appendix S1 for further details).

Because of reduced sample size and non-normal distributions, non-parametric validation analysis was conducted using ordinal MDS, which is a family of non-parametric methods that use geometric models to produce quantitative estimates of the similarity between all cases in a set[32] (Appendix S1). MDS and cluster analysis findings were compared by representing the cluster groups on the MDS map and scrutinizing the distributions.

Between-group comparisons

Once the whole sample was grouped by these methods into subgroups, the visual acuity and contrast sensitivity (Hiding Heidi) categorizations were compared with Fisher's exact test across all subgroups. For the subgroups completing the full assessment battery, the Sonksen LogMAR, LEA contrast sensitivity optotypes, and Frisby Stereotest scores were compared using the Mann–Whitney U test. Independent sample Student's t-tests were used to compare visual perception scores (TVPS-3 and Beery-VMI) between the subgroups completing the full battery of tests.

Within-group comparisons

Further within-group comparisons of the TVPS-3 and Beery-VMI scores were conducted. VCI standard scores were transformed to scaled scores for TVPS-3 subscale comparisons. Paired-sample Student's t-tests were used to compare each participant's VCI with their visual perception index and subtest score, and independent sample Student's t-tests were used to compare the index and subgroup scores to the normative data.

External validation

External validation was undertaken to compare all subgroups with 'external variables' using parametric/non-parametric tests as appropriate (two-sided significance level set at $p<0.05$, appropriate effect sizes reported).

For external variables, subgroup ages and IQ estimates were compared using Mann–Whitney U tests. CVI confirmation, sex, presence of movement disorder, and refractive error were compared using χ^2 tests. Parent questionnaire scores were compared between all subgroups using one-way analysis of variance. Other aetiological risk factors, neurodevelopmental disorders, and ophthalmological characteristics with more than nine presenting cases were compared using Fisher's exact tests across all subgroups. No formal post hoc testing was conducted because of the small sample.

Ethical approval

Ethical approval was granted by the Fulham National Health Service research ethics committee (reference 15/LO/0848). Written informed consent was obtained from each parent/guardian prior to participating in the project, including the research assessment and access to medical records. Children who were able to understand the implications of participating in the project were also asked for written assent to participate.

RESULTS

Information on participant ascertainment is provided in Appendix S1. The sample (n=63) had median age 8 years

Table 3: Neurodevelopmental and ophthalmological characteristics of the total sample and three classification subgroups

General characteristics	Total sample, *n*=63	Group A1, *n*=15	Group A2, *n*=28	Group B, *n*=20	Group A1, A2, and B comparison
CVI clinically confirmed	40 (68)[a]	9 (60)	16 (62)	15 (94)[a]	χ^2=10.06, *p*=0.006, *V*=0.42
Missing	4			4	
Median age, y:mo (IQR)	8:11 (6:8–12:1)	11:0 (8:11–14:11)	10:6 (7:1–12:3)	6:11 (6:0–8:9)	*H*(2)=14.37, *p*=0.001, η^2=0.21
Sex (male:female)	28:35	8:7	10:18	10:10	χ^2=1.59, *p*=0.45, *V*=0.16
Median IQ estimate (IQR)	87 (69–98)	98 (85–102)	87 (81.5–99.5)	48.5 (26.75–67.75)	*H*(2)=23.66, *p*<0.001, η^2=0.36

Aetiological risk factor for CVI[b]	Total sample	Group A1	Group A2	Group B	Group comparison
Periventricular leukomalacia	18 (29)	3 (20)	7 (25)	8 (40)	*p*=0.398, *V*=0.18
Intraventricular haemorrhage	13 (21)	2 (13)	7 (25)	4 (20)	*p*=0.675, *V*=0.11
Likelihood of hypoxia/ischaemia	13 (21)	4 (27)	6 (21)	3 (15)	*p*=0.729, *V*=0.11
Neonatal infection (confirmed)[c]	8 (13)	1 (7)	3 (11)	4 (20)	
Neonatal seizures[c]	6 (10)	0	2 (7)	4 (20)	
Hydrocephalusc	5 (8)	1 (7)	4 (14)	0	
Genetic (confirmed)[c]	3 (5)	0	3 (11)	0	
Cerebrovascular incident[c]	3 (5)	1 (7)	0	2 (10)	
Hypoglycaemiac	3 (5)	0	1 (4)	2 (10)	
Mean gestational age, weeks (SD)	33.92 (5.95)	34.40 (6.94)	34.04 (5.60)	33.37 (5.92)	*F*(59, 2)=0.13, *p*>0.05, η^2=0.01

Neurodevelopmental cooccurring condition[a]	Total sample	Group A1	Group A2	Group B	Group comparison
Movement disorder/cerebral palsy	29 (46)	2 (13)	11 (39)	16 (80)	
GMFCS level					χ^2=16.26, *p*<0.001, *V*=0.51
I	7	1	4	2	
II	8	0	4	4	
III	4	1	2	1	
IV	1	0	1	0	
V	9	0	0	9	
Current seizure disorder	12 (19)	1 (7)	4 (14)	7 (35)	*p*=0.117, *V*=0.08
Autism spectrum disorder[c]	9 (14)	4 (27)	4 (14)	1 (5)	
Attention-deficit/hyperactivity disorder[c]	3 (5)	2 (13)	1 (4)	0	
Developmental coordination disorder[c]	4 (6)	1 (7)	3 (11)	0	
Hearing impairment[c]	2 (3)	0	1 (4)	1 (5)	
Dyslexia[c]	2 (3)	1 (7)	1 (4)	0	

Ophthalmological characteristic	Total sample	Group A1	Group A2	Group B	Group comparison
Refractive error	38 (62)[a]	2 (13)	20 (71)	16 (89)[a]	χ^2=18.52, *p*<0.001, *V*=0.54
Missing	3			2	
Strabismus (manifest)	36 (59)[a]	2 (13)	18 (64)	16 (89)[a]	*p*<0.001, *V*=0.594
Missing	2			2	
Nystagmus	23 (38)[a]	2 (13)	9 (32)	12 (67)[a]	*p*=0.002, *V*=0.34
Missing	2			2	
Fundoscopy abnormal	18 (30)[a]	1 (7)	10 (36)	7 (41)[a]	*p*>0.05, *V*=0.30
Missing	3			3	

Data are *n* (%) unless otherwise stated. [a]For variables with missing data points, the percentage is calculated from the total valid responses. [b]May cooccur. [c]For variables with <10 participants reported to have the characteristic, statistical comparisons were not conducted. CVI, cerebral visual impairment; *V*, Cramer's V effect size; *H*, Kruskal–Wallis test; η^2, eta squared effect size; GMFCS, Gross Motor Function Classification System.

(interquartile range=6–12y, range=5–16y), 28 participants were male and 35 were female, with 36 recruited through hospitals and 27 self-referred. Four children lacked full ophthalmological assessment by the ophthalmologist (RB) because of difficulties in engaging in the examination, but they were included in the sample because no obvious impairments of the anterior (or peripheral) visual system were noted by him. Twenty-six participants (41%) had an existing clinical diagnosis of CVI from staff external or internal to our group; of the 59 participants able to participate in the full ophthalmology assessment, 40 (68%) reached the clinical criteria for a diagnosis of CVI by RB. Table 1 shows the vision function characteristics and distribution of clinical ranges of the whole sample. Twenty (32%) participants could not undertake the full battery of assessment and were classified as Group B, compared with the others (*n*=43, 68%) who were classified as Group A. The principal components analysis of the five input variables led to three factors that were interpreted as 'basic vision' (factor 1), 'higher-order vision' (factor 2), and 'three-dimensional vision' (factor 3), accounting for 87% of the variance in total and an acceptable fit of the data, with only 40% of residuals greater than 0.05 (Appendix S1).

Data-driven cluster analysis and validation

Using the five input variables a two-cluster solution was found, splitting Group A into Group A1 (*n*=15, 35%) and Group A2 (*n*=28, 65%) (Fig. S1, online supporting information). Statistical validation with MDS showed that a

two-dimensional solution was optimal (Stress-1=0.10, Dispersion Accounted For coefficient=0.99), and preserved the cluster analysis data structure (Appendix S1).

Subgroup comparisons of vision function

Participants were grouped according into Groups A1 and A2 (from cluster analysis), and Group B. Significant group differences were found according to the visual acuity and Hiding Heidi contrast sensitivity categories, with Group B having the lowest scores (Tables 2 and S1).

In the cluster analysis subgroups, Group A1 scores on TVPS-3 visual memory, spatial relations, visual sequential memory, and visual closure and the Beery supplementary task of motor-free visual perception were in the expected normative range, with no significant difference to normative data or participant VCI. TVPS-3 total was significantly lower compared to norms (but not in the 'clinically impaired' range) and not significantly different to participant VCI. TVPS-3 visual discrimination, form constancy, and figure ground were significantly lower compared to normative data (but not in the 'clinically impaired' range) and significantly lower than participant VCI. Mean Beery-VMI and the Beery supplementary task of motor coordination were significantly lower than the normative data (and in the 'clinically impaired' range) and significantly lower than participant VCI.

In Group A2, all TVPS-3 and Beery index and subtest scores were significantly lower than norms (and in the 'clinically impaired' range), and significantly below the participants' VCI scores (except TVPS-3 spatial relations; Tables 2 and S1). Group A1 scored significantly higher than Group A2 on TVPS-3 total, spatial relations, visual sequential memory, and visual closure and the Beery supplementary task of motor-free visual perception. There was no significant difference between Group A1 and A2 on TVPS-3 visual discrimination, form constancy, and figure ground, and Beery-VMI and the Beery supplementary task of motor coordination.

External variable comparisons

Statistical group differences were found between Groups A1, A2, and B in ophthalmological and neurodevelopmental characteristics, all ranging from lower to higher frequencies (A1 to B) with A2 as intermediate (Table 3). CP was the highest frequency neurodevelopmental disorder affecting 46% of the sample, but frequency and severity varied across the sample (Group A1 13%, Group A2 39%, and Group B 80%; no child was in Gross Motor Function Classification System level V in Group A1 and A2, but nine children were in this level in Group B). No significant intergroup differences were seen on the CVI Inventory or Pediatric Quality of Life Inventory scores, but all Pediatric Quality of Life Inventory scores were significantly lower than norms (Table 2).

DISCUSSION

This study is the first, to the authors' knowledge, to establish an empirical data-driven subgrouping method for visual functions in school-aged children with suspected or diagnosed CVI. The sampling decisions aimed to include the wide range of possible presenting visual symptoms, including children who were at the higher end of functioning and who had suspected or confirmed CVI. Before the study testing, under half of the sample had a confirmed diagnosis of CVI by our group or external clinicians. Before the study testing and without access to the 'higher-vision' tests, two-thirds of the sample reached the clinical diagnosis criteria for CVI according to our ophthalmologist (RB). The test analyses identified that the individual profiles of vision functions were heterogeneous and variable, and fell into three subgroups. The study provides first steps towards a validated subclassification method for the possible patterns of CVI.

Visual acuity was variable across the sample, with half of participants having visual acuity impairment ranging from 'socially significant' (logMAR 0.3–0.49) to severe visual impairment (worse than logMAR 1.0).[18] Nearly half had normal visual acuity and visual fields (of the 71% of the sample with valid visual field results), highlighting the fact that measurement of acuity is not necessarily sufficient to understand the full spectrum of vision dysfunctions of this population.[1,14,33] Of the two-thirds of participants able to complete the full assessment battery, a principal components analysis provided construct validity to the measures selected as input variables. Three factors were identified to account for the majority of the variance together and individually, interpreted as 'basic vision', 'higher-order vision', and 'three-dimensional vision', as predicted by the literature. Using these input variables, two subgroups (Groups A1 and A2) were identified through cluster analysis. They also presented as separable in MDS, supporting the notion that cluster analysis revealed a natural structure in the data rather than being a random finding.

The profile analysis of each group showed that Group A1 had visual acuity, contrast sensitivity, and most visual perception index and subtest scores in the normative average range with significantly higher scores than those in Group A2. A number of visual perception subtests (TVPS-3 visual discrimination, form constancy, and figure ground, and Beery-VMI and the Beery supplementary task of motor coordination) were on average lower compared to normative data, and had no significant difference in means to Group A2. At group level, these areas of visual perception appeared to be a selective weakness as they were significantly lower than their individual cognitive VCI scores and reflected a subtest profile suggestive of 'dorsal stream' difficulty in the CVI literature, including visuo-motor integration difficulties.[1,30]

Group A2 showed greater weaknesses across vision functions, with one-third of participants having mild-to-moderate visual acuity impairment and the majority having weak/absent stereopsis. All of their TVPS-3 visual perception test scores (except spatial relations) and Beery visuomotor scores were below the norms at group level and in the clinically impaired range, and were significantly lower than

their individual VCI scores. This pattern of visual perception and visuomotor difficulties could reflect more severe or widespread difficulties[1,30] than in Group A1.

Group B were in the lower-functioning range and could not be entered into the cluster analysis. They were statistically lower in the visual acuity range than the Group A subgroups, with 80 per cent in the moderate visual impairment to blind range and with poor contrast sensitivity. Even those in the moderate visual impairment range could not undertake the full assessment battery because of constraints in cognition and motor status.

The typology of vision dysfunctions in this sample therefore fell into three subgroups with discrete profiles and a continuous spectrum of severity including visual acuity reduction from Group A1 to B (in direction of greater severity, with Group A2 as intermediate). Although visual fields had over one-quarter of the sample with missing data and too much missing data to be included in the cluster analysis, the spectrum across the sample subgroups (Group A1 to B) was in a similar direction of severity (with Group A2 as intermediate).

External validation of the three subgroups also showed discrete profiles with a similar spectrum and direction of severity from Group A1 to B (with Group A2 as intermediate), according to the frequency of ophthalmological (refractive errors, strabismus, and nystagmus) and neurodevelopmental characteristics (movement disorders). CP was the highest cooccurring neurodevelopmental impairment as anticipated in the literature,[33] but frequency and severity ranged from Groups A1 and A2 to Group B (with the majority having CP and almost one-half of participants in Gross Motor Function Classification System level V in the latter group). However, all groups had lower mean gestational age with no significant within-group differences, highlighting preterm neonatal status as a risk factor across all groups.

These combined results provide empirical data to support the theory that the construct of CVI is an identifiable multidimensional neuro-ophthalmological/neurological presentation, which affects diverse visual functions ranging from basic visual acuity to higher-order visuocognitive perception, as reported in the literature. From a latent construct stance, the factors of basic and higher-order vision and three-dimensional vision are separable. This complex disorder can be further subdivided into discrete profiles associated with 'external variables' of aetiological risk factors, neurodevelopmental disorders, and ophthalmological characteristics that correspond to the associated vision function subgroups. However, it also appears to be highly likely to be a continuous spectrum condition with each group manifesting more severe variants of similar visual function defects and other aspects of brain function, including cognition and movement, in the direction of Groups A1 to B (with A2 as intermediate). This concurs with Philip and Dutton,[1] who argued for a classification system from higher functioning to lower functioning, including vision and cognitive/motor status.

Further support for the construct of CVI as an integral condition, whatever its severity, is the finding that the groups did not differ in their most frequent aetiological risk factors of periventricular leukomalacia, intraventricular haemorrhage, and the likelihood of hypoxia/ischaemia. Nevertheless, hypoxia/ischaemia was most prevalent in Group A1 (which could be explained by the sensitivity of 'dorsal' pathway development at birth[1,34]) and periventricular leukomalacia in Group B, suggesting some preferential risk for each typology, although further research is needed to substantiate this. Irrespective of group category, the adverse functional impact of CVI appeared high and parent questionnaires reported a broad range of vision-related difficulties in everyday activities and low quality of life, with no statistical difference in scores between the three groups.

Study limitations may affect the generalization and interpretation of findings. The recruitment strategy was intended to also identify higher-functioning children who may not present at specialist clinical services and, as such, sampling may have had participant overinclusion with parental self-referral and external clinical diagnoses of CVI (which may use different diagnostic criteria) from outside the hospital accepted. Clinical examination by RB confirmed two-thirds of the subgroup as reaching a diagnostic threshold for CVI according to his criteria, but this might have increased for some of the other children if he had had access to the 'higher-vision' scores from this study at the time of examination. Unfortunately, it was beyond the scope of this study to investigate individual participant vision profiles. Group B may underrepresent the total population at the severe end, as rare cases of intellectually able children with severe acuity reduction but no motor abnormalities (e.g. occipital lobe pathology) are occasionally seen in clinic. The selection of tests and input variables successfully differentiated the higher-functioning group into two clusters with the exception of contrast sensitivity. Contrast sensitivity was mainly in the normal range (this may have been because of ceiling effects) in Groups A1 and A2, but it did differentiate between Groups A and B.

Although minimum sample size recommendations vary,[13] cluster analysis would ideally be conducted with a larger sample than the 43 children in this study. Because of this reduced sample size and skewed distributions of some vision data, the subgrouping process had to be undertaken in two stages, including non-parametric validation. The missing visual field data prevented inclusion because of a lack of perimetry assessment reliability, but field deficits were common in the children who participated in testing (47% with valid results) and may have been informative.[1] In addition, certain vision functions that have been reported in the literature, including picture recognition, were assessed but were not included in the cluster analysis, which might be important for future profile analysis and subtyping. The CVI Inventory and the Pediatric Quality of Life Inventory questionnaires were used, but it is not known how cooccurring disabilities (like

motor impairment) may also impact on everyday activities and could have influenced parent responses. Additionally, some reported cooccurring paediatric conditions (autism spectrum disorder or attention-deficit/hyperactivity disorder) could possibly present with some symptoms/characteristics (e.g. poor face recognition or weaker visual attention) that might overlap with those of CVI. The order of when the previous paediatric or CVI diagnoses were made in each child is not known, and some diagnostic 'overshadowing' remains possible with symptoms from one causative aetiology attributed to another.

Because of the scope of this study, the research sample was limited to school-aged children with diagnosed or suspected congenital CVI. Further research will be needed to investigate whether these findings can be generalized to all children with potential CVI, including late-acquired causes of CVI or the earlier preschool age range. It will also be important to investigate how findings may relate from the group level to the individual child. Although distance visual acuity is the criterion standard assessment of acuity, all testing in this study, including visual acuity, was conducted at near distance, as near vision was crucial for establishing whether the children had sufficient vision to undertake the visual perceptual tests and is relevant for school-related desk-top learning. Future research could investigate how distance visual acuity might be useful instead of near visual acuity in the subgrouping and classification.

A number of clinical implications arise from these findings. The study results suggest that this core standard test battery, using previously validated clinical tests, could help identify children's profiles and aid subgrouping. It paves the way for an integrated and systematic ophthalmological and neurodisability assessment process, with the aim of greater consensus and reliability in the multidisciplinary diagnostic process. Future clinical and research directions may use the same methods to generate clinical thresholds, and the identification of an algorithm to aid in the diagnostic and subtyping process, with 'at risk' populations (such as those with CP or preterm) to establish prevalence of subgroups.

The diagnostic cut-offs for each subgroup will need to be established, as well as the diagnostic boundaries for each condition and whether a child should be viewed as having 'clinical-threshold CVI' if they are at the outer limits of the spectrum as in Group A1. In Group A1, only higher-order visual functions were affected and only visuomotor integration (Beery-VMI and the Beery supplementary task of motor coordination) was in the 'clinically impaired' range. When interpreting the individual child's basic and higher-vision profile, it will be pertinent to consider the child's overall assessment profile rather than single visual perception subtests alone, which have more limited psychometric reliability. We did not consider the educational and adaptive impact of their visual dysfunctions on individual children; for instance, some children may be having significant problems in the classroom, such as reading or handwriting, and with everyday life skills, which would need consideration as part of a comprehensive diagnostic process. The diagnostic issues are beyond the scope of this study, but continue to need serious consideration because of the degree to which entitlement to special educational needs provision and support is extended to individual patients. Of future interest is the functional impact of these visual dysfunctions on the child, their changing needs over time, and whether this vision metric test battery involving static materials fully captures the functional challenges reported in a dynamic and visually complex environment.

The creation of a classification system is important for testing and refining potential intervention strategies, as the current construct of CVI has been too broad to influence management. The children in Group A1 or A2 (with normal/mild-to-moderate visual acuity reduction) may be missed as having visual problems in education[35] and often struggle to access support, but simple recognition of figure ground discrimination problems, for example, may allow modification of education materials to render them more visible to a child. Therefore, we conclude that our subgrouping method and prototype classification system represents a step forward in understanding and improving the lives of children with CVI.

ACKNOWLEDGEMENTS

The authors wish to thank the parents, children, and young people involved for their generous participation; the assistance of voluntary organizations, including the CVI Society England, in recruitment; Professor Jugnoo Rahi and Dr Alison Salt who were involved in the original design and conception of the study, and were coapplicants for funding; Professor Lea Hyvarinen, Professor Janette Atkinson, Professor Oliver Braddick, Professor Neil Marlow, and Associate Professor Cathy Williams for assisting in the design of methods and test usage; Philippa Cumberland for vision classification advice; and Professor Mario Cortina Borja for statistical guidance in relation to cluster analysis and MDS. This research was funded by a doctoral research studentship award (to HS) from the Ulverscroft Foundation Vision Research Group. It was also supported by the National Institute for Health Research Clinical Research Network and the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital National Health Service Foundation Trust and University College London. The funders had no further involvement in study design, data collection, data analysis, manuscript preparation, and/or publication decisions. The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Vision characteristics of the three classification subgroups (full version)

Appendix S1: Additional methodological and statistical details.

Figure S1: Dendrogram of cluster analysis.

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