Final version published in Developmental Medicine Child Neurology
Dale N, Sakkalou E, O'Reilly M, Springall C, De Haan M, Salt A. Functional vision and cognition in infants with congenital disorders of the peripheral visual system. *Developmental Medicine and Child Neurology*. PMID 28439876 DOI: 10.1111/dmcn.13429

Functional vision and cognition in infants with congenital disorders of the peripheral visual system.

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Acknowledgements:

This research was jointly funded by Fight for Sight, Royal National Institute of Blind People (RNIB), and Great Ormond Street Hospital Children's Charity to XX. It was also supported by the NIHR Clinical Research Network and the NIHR Biomedical Research Centre at Great Ormond Street Hospital NHS Foundation Trust and University College London. XXX is supported by Great Ormond Street Hospital Children's Charity. RNIB was involved in the original conception of the study design; the funders have had no further involvement in study design, data collection, data analysis, manuscript preparation and/or publication decisions. The authors have declared no competing or potential conflicts of interest. The authors thank infants and families for their generosity in assisting with the research and to Hanna Sakki for her assistance on the project.

Abstract

Aim

To investigate how vision relates to early development by studying vision and cognition in a national cohort of one year old infants with congenital disorders of the peripheral visual system (CDPVS) and visual impairment (VI).

Method

Cross sectional observational investigation of a nationally recruited cohort of infants with 'simple' and 'complex' CDPVS, entry age 8-16 months. Vision level (Near Detection Scale-NDS) and non-verbal cognition (Sensorimotor Understanding (SMU), Reynell Zinkin Scales) were assessed. Parents completed demographic questionnaires.

Results

90 infants, mean age 13 months; 25 (28%) with profound VI (light perception at best) and 65 (72%) with severe VI (basic 'form' vision). NDS correlated significantly with SMU DQs in the 'total', 'simple' and 'complex' groups (all $p<0.001$). Age and vision accounted for 48% of SMU variance. Infants with profound VI, especially in 'complex' CDPVS with known brain involvement, showed the greatest cognitive delay.

Interpretation

Lack of vision is associated with delayed early object manipulative abilities and concepts; 'form' vision appeared to support early developmental advance. This paper provides baseline characteristics for cross sectional and longitudinal follow up investigations in progress. A methodological strength of the study was the representativeness of the cohort according to national epidemiological and population census data.

Shortened working title: Vision and cognition of visually impaired infants

What this research adds:

- At one year level near detection vision is strongly associated with cognitive outcome.
- Infants with visual impairment have difficulty acquiring early manipulative abilities and object concepts, particularly if they have no vision.

Infants with congenital vision disorders are recognised as a highly vulnerable clinical population, but the functional and developmental outcomes are remarkably understudied [1]. Severe visual impairment (VI) impacts adversely on all aspects of early development compared to normally sighted comparison groups with greatest developmental delay and difficulties reported in the most profound VI [2-13]. Previous research has been limited by unsystematic measurement of low vision, heterogeneous samples and small scale observational samples or retrospective clinical series, making interpretation and comparisons between research groups difficult [10, 13]. Prospective longitudinal research is urgently needed to understand the early natural history, factors and mechanisms influencing the developmental process [10, 13, 14]. However, key challenges for research are the low incidence rates of the population, geographical dispersion and problems in early detection and identification, wide variation in congenital vision disorders and within group heterogeneity and frequent co-occurrence with other disabilities [1, 8, 13 - 16].

Congenital vision disorders are rare with conservative estimates of 4-5 per 10,000 with 'blind/severe' VI in the first year of life –UK [15], leading to significant challenges and costs in recruiting a sufficiently powered infant cohort within realistic time limits. National identification with sufficient population density is an essential starting point as no single health centre has the patient volume required. The timing of diagnosis is, nevertheless, uncertain depending on recognition of early physical or behavioural signs followed by a prolonged process of ophthalmological and paediatric investigations[15, 16]. Recruitment through national surveillance registers is problematic as they may be incomplete or biased with an over-inclusion of children with multiple impairments or delays in registration by professionals [1, 15, 16]. About half of childhood vision disorders originate in the retro-chiasmatic cerebral visual pathways, with a high rate (60%) of additional non-ophthalmic impairments [15] which are potentially confounding influences on early development [13]. The rarer subgroup of infants with congenital disorders of the peripheral visual system (CDPVS) were therefore selectively targeted in this study to investigate the impact of VI on development and learning. This group could be further sub-divided into 'potentially simple' ie with no known brain involvement (eg aniridia alone) or 'potentially complex' ie. with known brain involvement in the paediatric diagnosis (eg aniridia in WAGR syndrome) [11,13] . The 'potentially simple' sub-group, which has been shown previously to have only 17% with global intellectual disability [13], was anticipated as having the least non-ophthalmic confounding influences and therefore the primary group of interest.

This study set out to address the above problems robustly and to recruit a sufficiently large and representative infant sample for future analyses (XXXX, in progress). It is the first study using standard measures of vision and cognition prospectively in infants with CDPVS in contrast to a retrospective clinical records study [11]. According to the literature, it is predicted that functional vision is associated with early cognitive outcome, with greatest delay in infants with no 'form' vision (profound VI). The objective of this paper is therefore to describe the functional vision and cognitive characteristics and associations in infants with CDPVS within a sample that is checked for its epidemiological and population representativeness[17] as a national cohort. The cohort will be compared with normative developmental expectations for fully sighted children of the same age to establish developmental pattern and needs for this age period.

Method

Design of study

Cross sectional observational investigation at first time point (T1) of a prospective longitudinal study with a nationally recruited cohort: XXXXX (XXXX et al, in progress).

Setting

Hospital research site, home based or both (n=61, 25, 4 respectively) across the UK with the majority from England; entry to study 2011-2014.

Participants

Eligibility criteria: infants with CDPVS i.e. ophthalmological disorders of the globe, retina and anterior optic nerve to optic chiasm without ('potentially simple') or with ('complex') known central nervous system involvement in the vision or paediatric diagnosis and chronic VI which is in the severe-profound level at time of recruitment [11 13]. All infants had a classifiable vision disorder (ICD-10) according to medical diagnosis through ophthalmology departments. Age at entry: 8-16 months, which is a reliable age for systematic near detection vision and developmental assessment[8] and allowing for variability in age of diagnostic identification.

Exclusion criteria: clinically diagnosed neurological motor or hearing impairment, retinopathy of prematurity, severe prematurity and parents who did not speak sufficient English to complete questionnaires.

Recruitment strategy Single site specialist hospital research centre undertook direct recruitment using a national open enrolment strategy. Thirty one NHS hospitals with Local Collaborators from paediatric ophthalmology joined as Patient Identification Centres (UK CRN portfolio no. xxxxx). Participants were identified through paediatric ophthalmology, paediatric neurodisability/developmental vision, paediatric health visiting/ early years and child development services, specialist educational visual impairment services, national voluntary organizations and self-referral.

Ethical approval was obtained from Health Ethics Committee (Bloomsbury NHS REC no. xxxxxxx) and met standards required by the guidelines set out by the Social Research Association (SRA). Written informed consent was obtained from parent participants for participation and publication. Data collection and protection followed current guidance.

Procedures and measures

Infant participants attended a half day assessment session. Vision level was measured using the Near Detection Scale- NDS[18]: 10 point scale ranging from no light perception (0) to 0.1 cm 'lure' (9) according to visual fixation on diminishing sized lures at standard near distance (30 cm). Two vision level categories were derived of 'profound' VI (points 0-1, light perception at best) and 'severe' VI (points 2-9, 'form' vision of differing levels). For descriptive purposes, Keeler Acuity Cards (KAC) [19] were attempted at standard near distance on all infants with vision greater than point 1 (NDS). Sensorimotor understanding (SMU) was assessed by a trained developmental psychologist (XX 80%, XXX 20%) in a semi-standardised play based assessment using the Sensorimotor Understanding subscale of the Reynell Zinkin Scales (RZS) for young children with VI [2, 3]. Parents filled in a demographics questionnaire leading to classification of geographical location, socio-economic status (SES), maternal education and black/ ethnic minority identification (BME) according to definitions and methods of the Office for National Statistics UK [17]. Vision disorder diagnoses were classified according to a UK national epidemiological framework [15].

Bias Reports of vision and paediatric diagnoses in non-medical referrals were compared to available medical reports to ensure accuracy and any discrepancy was investigated. Observational assessments were video-recorded to permit post-assessment scoring and further consensus scoring with senior clinicians (XX, XX) in uncertain cases.

Study size

129 infants were ascertained (129% of planned sample) and 100 (77.5%) consented to participate reaching target sample size. One was excluded retrospectively because of emerging motoric impairment. As this paper focuses on vision and developmental measures in children with CDPVS, 9 children with cerebral vision disorders who consented to participate were not included in this analysis. Reasons for non-participation (n=29) included parent decided not to take part (n=12), parent could not be contacted (n=5), expression of interest form not returned (n=3), parent not available for first appointment (n=5) parent did not attend first appointment (n=4).

Statistical methods

Data was double checked for accuracy and missing data was inspected. Frequency analyses were computed on non-missing cases only and number of missing cases declared. Individual response items with greater than 15% missing data and other variables with greater than 20% missing data were excluded. Descriptive statistical analyses were undertaken for the nominal data of the medical vision disorders and demographic characteristics and the ordinal data of the continuous NDS (highest point achieved per participant) and SMU subscale (total raw score of summated items achieved per participant). Distributions of the NDS and SMU scores were examined for normality by plotting on histograms, using Kolmogorov-Smirnov test and examining skewness and kurtosis/ standard error (<1.96 within normal limits). Parametric or non-parametric statistics were used depending on normative distributions. The ratio developmental quotient (DQ) – SMU was computed by converting the summated raw score of the SMU to the mid-point of the age equivalent level on the 'sighted' norms[3] and dividing by chronological age x 100[11]. Partial correlation and multiple regression statistics were used to compute the independent effects of age and vision level (PVI, SVI) on SMU scores. Analysis of variance was used to compare SMU scores between the different anatomical categories (globe, retina, optic nerve). To control for the effect of multiple comparisons on p-values, the Benjamini-Hochberg false detection rate procedure was adopted; the results remained significant after the adjustment in p-values. All reported p-values are 2-tailed.

Results

Participants

Ninety infants with CDPVS conditions in the 'total'group (69 'simple' and 21 'complex' sub-groups) were assessed at mean age 13 months (range 7-17 months). Chronological age was normally distributed in the total and sub-groups. There was no significant difference in age, gender, gestational age or birth weight between the sub-groups (see Table 1).

Child characteristics: vision level and SMU

NDS scores showed a bimodal distribution in the total and sub-groups, ranging from 0-no light perception to 9-0.125 cm 'lures'. Of the total group 25 (27.8%) had profound VI and 65 (72.2%) severe VI (see Table 1). In the severe VI sub-group, 34 (52.3%) achieved ratings on the KAC (range 0.18 - 6.5 cycles per degree at 38 cm), the other 31 were unable to give a reliable measure. With the exception of five children, the remaining scored below 2.9 cycles per degree (approximate Snellen equivalent of 6/60 or logMAR 1.0).

SMU raw scores were normally distributed in the total and sub-groups and had no outliers (see Table 1). Parametric analyses showed significant correlations between age and SMU raw scores in the total (Pearson r=0.53, p<0.001), 'simple' (r=0.53, p<0.001) and 'complex' (r=0.52, p<0.05) groups. Partial correlation between birthweight and SMU DQ in total group, when controlling for vision level (PVI, SVI) was non significant (r 0.02, p>0.05). There were moderate correlations between age and SMU raw score, when controlling for vision level (total group r 0.58 p<0.001, 'simple' r 0.57, p<0.001, 'complex' r 0.62, p<0.01). NDS correlated significantly with the SMU DQs in the 'total', 'simple' and 'complex' groups (non-parametric Spearman r=0.58, r=0.54, r=0.69, all p<0.001). See Figure 1. The mean DQs were significantly lower in the profound than severe VI sub-groups in the total, 'simple' and 'complex' groups (equal variances assumed, total $t(88) = 4.34$, p<0.001, d=1.03, 'simple' $t(67)=2.88$, p<0.01, d=0.80; 'complex' $t(19)=3.51$, p<0.01, d=1.74). Non-parametric comparisons also reached significance level for all groups. A multiple hierarchical regression showed age and vision level (PVI, SVI) accounted for 48% (R^2= 0.48) of variance in SMU raw scores. Vision level explained 20% after controlling for age ($F(2, 87) = 40.28$, p<0.001). Standardised beta coefficients were β= 0.51, p<0.001 for age and β =0.45, p<0.001 for vision level.

According to the anatomical site of the visual disorder, i.e. globe, retina and optic nerve (see Table 2), the mean DQs were 91.9, 94.9, and 84.1 respectively (n=86, 4 participants in the 'other' category were not included). The SMU DQs were normally distributed in each anatomical group and according

to the ANOVA, there was no significant difference in mean DQ between the three groups, $F(2, 83) = 1.83$, $p = 0.17$.

Representativeness of the sample compared with national indicators

Table 2 shows the incidence of discrete vision disorders in the total group (in the case of multiple disorders a primary one was selected per child); 16 (76.2%) of the 'complex' sub-group were septo-optic dysplasia and the others included chromosomal 14 deletion, microcephaly, genetic mutation with cerebellar vermis abnormality, DiGeorge syndrome. The proportions of globe, retina and optic nerve disorders were distributed fairly evenly (38.9%, 34.4% and 22.2%) and were closely comparable to the national epidemiological data.

Table 3 reveals the diverse referral sources and geographical locations of the participating and non-participating infants and showed that they were roughly similar. SES data was missing from 30 parents (33%) and therefore SES could not be computed for the sample. Maternal education and BME data showed representation in all categories with some variation according to expected population census proportions (Table 4).

Discussion

This study reports on the first national cohort of one year old infants with very rare congenital disorders of the peripheral visual system (CDPVS) recruited prospectively for longitudinal developmental research. The cohort was shown to be representative of these congenital vision disorders according to national epidemiological data and therefore provides a unique opportunity to investigate the impact of congenital VI on early sensorimotor cognitive development. By one year, the infants' vision levels ranged from profound to severe VI and almost all were below the Snellen equivalent of 6/60 (logMar 1.0). About a quarter of the infants were profoundly VI with light perception at best. The infants' near detection vision level was significantly associated with their SMU DQs according to sighted norms, with infants with the most profound VI showing the greatest cognitive delay compared to normative sighted expectations.

Providing further empirical support for the value of the RZS for infants and toddlers with VI [2, 3], chronological age significantly correlated with SMU raw scores. This highlighted that young children with VI do make progress developmentally in sensorimotor cognitive development at this age and that the RZS is sufficiently sensitive for measuring progress. However, there was a strong positive correlation between NDS and SMU DQs, highlighting the relationship of VI and differing levels of functional 'form' vision in early sensorimotor progress. Infants with profound VI were well below sighted expectations with a mean DQ of 83.9 in the 'simple' group. A significantly higher mean DQ (97.8) in infants with severe VI suggested that having basic 'form' vision supported mastery of early manipulative abilities and object concepts [2, 3, 9, 10, 11, 20- 22] close to typically sighted expectations. Even though the infants had very low levels of vision which were insufficient to see detail of objects, basic vision stimulus appeared to facilitate the neural and/or conceptual basis for object learning and manipulation. In contrast, infants with PVI were relying on tactile stimulus for hand manipulation and this early haptic learning appeared less efficient for object task performance. The need for compensatory support and mechanisms is therefore likely to be critical for infants with PVI during the first and then second year of life. These findings argue for the importance of early vision promotion in the *first year of life* as any progress in 'form' vision appeared to be beneficial for infancy object related learning [4].

Age and functional vision level accounted for nearly half (48%) – with vision level about a fifth– of the variance of the SMU raw scores. Other multi-level factors which may account for the remaining SMU variance and very wide range of DQs (in both the PVI and SVI sub-groups) are currently under investigation and will be reported in forthcoming papers. Some children with PVI in the 'potentially simple' sub-group were in the high DQ range suggesting that high early cognitive potential could

compensate for lack of vision at this age. As SMU is potentially a proxy measure for early brain integrity the infants with the lowest DQs were possibly showing emerging learning difficulties and the stability of these differences at 2 and 3 years outcome will be investigated in future papers. The 'potentially simple' sub-group was made up of highly heterogeneous disorders with potentially different outcomes and it is possible that in some children as yet unidentified genetic causes of additional learning difficulty were influencing outcome. However there is no clearly established genotype-phenotype relationship for many of the disorders and developmental outcome can be highly variable between and within disorders (eg Leber's amaurosis). The more delayed mean performance of those with profound VI might reflect a genetic bias; however the distribution of profound and severe VI in nine different vision disorders argues against the influence of any single eye disorder. No evidence was found to relate learning outcome to basic anatomical disorder with no significant difference in mean SMU DQs between the anatomical categories of globe, retina and optic nerve disorders in the total and 'simple' groups. With the exception of optic nerve hypoplasia, none of the children in the 'potentially simple' group would have had routine neuroimaging so it is not known whether some of them also had undetected brain lesion involvement[23].

The secondary group of 'complex' CDPVS and especially those with profound VI was shown to be highly vulnerable with a low mean DQ of 64 (in line with trends reported in Vervloed et al[10]). As anticipated, the 'complex' Total ,SVI and PVI subgroups had significantly lower DQs than the equivalent 'potentially simple' Total and subgroups, suggesting greater CNS involvement and non-ophthalmological impairment in the 'complex' group. Notably, the majority of the 'complex' group had septo-optic dysplasia but to date genotype-phenotype correlations have not been established [24]. The evidence from this paper of developmental vulnerability and challenges in learning about the physical environment reinforces the need for informed specialised early intervention from as early as possible to reduce cumulative risks [13, 14, 22, 25].

The national open enrolment strategy was effective in recruiting the largest cohort reported to date of rare CDPVS disorders (n=90) within a narrow infancy entry age. This was feasible using a wide health-education recruitment strategy within a population density of nearly 700,000 live births per year (England, Wales) [17]. The evidence compared to a UK national epidemiological study [15] suggested that the cohort was largely representative of the childhood vision disorders (CDPVS) population although the studies used slightly different accounting methods. The cohort included similar proportions of retina and optic nerve disorders but a higher proportion of whole globe disorders which is likely to reflect a sampling commitment to ascertaining infants with profound VI. The absence of glaucoma and cataract conditions may reflect improving medical treatments and the potentially reversible nature of these conditions [15] and possibly the reluctance of families to participate or clinicians to recruit given the high level of surgical and medical intervention in the first year of life.

The geographical, maternal education and ethnic minority patterns of the cohort covered all categories of population census data [17], thereby suggesting that the cohort is relatively representative. Nonetheless, there were fewer families from the north of England, which may reflect a participant bias to those who lived closer to the hospital research site in southern England. Unfortunately there was too much missing data to compute the SES representativeness and it is not known if there was a reporting reluctance of those in less skilled employment or unemployment in the 30 parents who did not respond or partially responded. The lower incidence of Asian families compared to the national epidemiological data [15] might reflect the exclusion of more complex medical disorders which are more highly represented in this ethnic group[15] and also lack of fluency of English in parents. The higher level of maternal education than in population census data suggests a possible participant bias towards higher SES categories with a recognised greater ease in recruiting these parents into vision research studies [26].

The strength for generalisability of this study is the size and representativeness of a national cohort of infants covering heterogeneous CDPVS conditions. Of possible limitation, a small proportion of infants were at the upper limit of the NDS causing possible ceiling effects. The RZS has been criticised as lacking item variation at infancy level which may reduce reliability and cause floor

effects [10]. Although others have demonstrated that the RZS has adequate stability and internal consistency at 1 year [8, 10], the RZS has to date lacked psychometric standardisation including with the CDPVS population[11, 13]. Future longitudinal analysis with this cohort will permit the development of new test norms with the 'simple' CDPVS group as the best reference group and also consideration of norms for the PVI and SVI subgroups [11, 13]. Derivation of SMU DQs from the 'sighted' norms (though limited and possibly outdated) appears to have reduced the risk of over-estimation of development that has been reported previously with the 'blind' and 'partially sighted' norms and was useful in demonstrating early vulnerability in the total cohort and in particular in the profound VI subgroups compared with sighted expectations [10, 11]. The secondary 'complex' CDPVS group should be considered cautiously because of lesser frequency and a predominance of septo-optic dysplasia.

In summary, the functional vision, non-verbal cognitive and demographic characteristics of a representative national cohort of infants with CDPVS have been established. Age and vision level were shown to be strongly related to SMU outcome at one year. The longitudinal follow up of the cohort at two and three years is in progress and will be able to determine the importance of these early patterns for subsequent advances in vision, cognition and other development, including the risk of developmental setback and field influences of early childhood intervention [13]. These baseline study findings could be used for future benchmarking in randomised controlled intervention trials, which are urgently required.

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Table 1. Infant characteristics and comparisons in total, 'simple' and 'complex' CDPVS groups

	Total (n=90)	**Simple (n=69)**	**Complex (n=21)**	**Comparisons (simple/complex)**
Age				
Mean months *(SD)*	13.0 (*2.5*)	13.1 (*2.6*)	12.8 (*2.3*)	t(88)=.51, p=0.61
Range	7-17	7-17	8-17	
Gender				
Male (N)	49	41	8	$\chi^2(1, N=90)= 3.0$,
Female (N)	41	28	13	$p = 0.09$
Ratio	1.2:1	1.5:1	1:1.6	
Birth Weight				
Mean kg (SD**)**	3.31 (0.57)	3.36 (0.51)	3.15 (0.74)	t(23)=1.15,
Range	1.82-4.32	1.82-4.31	2.01-4.32	p=0.24
Gestational Age				
…..Mean wk (SD)	39.44 (2.02)	39.52 (1.82)	39.16 (2.61)	U=586.00, p=0.81
Range	32-43	34-43	32-42	
Vision level				
PVI (N)	25	18	7	$\chi^2(1, N=25)=$ 0.30, p=0.58
SVI (N)	65	51	14	$\chi^2(1, N=65)=$ 1.17, p=0.73
Ratio	1:2.6	1:2.8	1:2	$\chi^2(1, N=90)=$ 0.42, p = 0.52
Near Detection Scale				
Range	0-9	0-9	0-9	
SMU Raw Score				
Mean *(SD)*	10.1 (*3.0)*	10.5 (*2.9)*	9.1 *(2.9)*	t(88)=1.94,
Range	5.0-16.0	6.0-16.0	5.0-14.0	p=0.06
SMU DQ Score				
Mean *(SD)*	91.8 *(20.0)*	94.2 *(18.5)*	84.0 *(23.2)*	t(88)=2.08,
Range	43.6-138.6	43.6-138.6	51.5-134.6	p<0.05, *d*=0.49*
PVI				
Mean *(SD)*	78.3 *(18.1)*	83.9 *(16.7)*	63.9 *(13.4)*	U=17.0, Z=2.78,
Range	51.5-129.1	61.8-129.1	51.5-89.5	p<0.01*
SVI				
Mean *(SD)*	97.0 *(18.4)*	97.8 *(17.9)*	94.0 *(20.5)*	U=300.0, Z=0.91,
Range	43.6-138.6	43.6-138.6	55.1-134.6	p=0.36

* p<0.05

Table 2. Frequency and percentage of visual disorders in CDPVS group according to anatomic site affected and vision level category, compared to UK population epidemiological data

	Visual disorder (grouped according to primary anatomical site affected)	N=90 (%)	PVI (n=25)	SVI (n=65)	UK national epidemiological data [15] N=439 (%)
1	***Whole globe and anterior segment***	**23 (25.6%)**	**9**	**14**	**29 (7%)**
1.1	Microphthalmia/anophthalmia	13 (14.4%)	7	6	
1.1.1	- *additional coloboma*	*(inc. 4)*	*0*	*4*	
1.2	Anterior segment dysgenesis	4 (4.4%)	1	3	
1.3	Coloboma-multiple sites	4 (4.4%)	0	4	
1.4	Other	2 (2.2%)			
1.4.6	- Persistent hyperplastic primary vitreous	2 (2.2%)	1	1	
2	*Glaucoma (primary and secondary)*	**0**			**13 (3%)**
3	*Cornea (sclerocornea and corneal opacities)*	**0**			**7 (2%)**
4	*Lens (cataract or aphakia)*	**2 (2.2%)**	**0**	**2**	**21 (5%)**
5	*Uvea*	**10 (11.1%)**	**0**	**10**	**12 (3%)**
5.1	*Aniridia*	10 (11.1%)	0	10	
6	***Retina***	**31(34.4%)**	**9**	**22**	**126 (29%)**
6.2	Retinal and macular dystrophies	14 (15.6%)			
6.2.1	- Cone	1 (1.1%)	0	1	
6.2.2	- Cone-rod	2 (2.2%)	1	1	
6.2.4	- Leber's amaurosis (Early onset retinal dystrophy)	9 (10%)	6	3	
6.2.7	- Congenital stationary night blindness	1 (1.1%)	0	1	
6.2.9	- Unspecified macular dystrophy	1 (1.1%)	0	1	
6.3	Ocular-cutaneous albinism	7 (7.8%)	0	7	
6.6	Retinoblastoma	1 (1.1%)	0	1	
6.7	Other	9 (10%)			
6.7.2	- Dysplasia (inc retinal folds and Norrie disease)	4 (4.4%)	2	2	
6.7.7	- Ocular albinism	4 (4.4%)	0	4	
6.7.8	- Familial exudative vitreoretinopathy (FEVR)	1 (1.1%)	0	1	
7	***Optic nerve***	**20 (22.2%)**	**7**	**13**	**123 (28%)**
7.1	Hypoplasia	19 (21.1%)			
7.1.1	- Isolated	3 (3.3%)	1	2	
7.1.2	- Septo-optic dysplasia (Complex)	16 (17.8%)	6	10	
7.2	Atrophy	1 (1.1%)			
7.2.1	– Primary	1 (1.1%)	0	1	
9	***Other***	**4 (4.4%)**	**0**	**4**	**8 (2%)**
9.1	Idiopathic nystagmus	4 (4.4%)	0	4	

Only primary site affected in cohort is recorded in this table and other sites may have been affected in the individual child. National epidemiological data includes multiple sites affected per child [15] abbreviated.

Table 3. Infant characteristics of the total sample and non-participants at referral: recruitment source, mean age, gender and geographical region

Infant variables	**Sample (n=99) n (%)**	**Non-participants (n=29) n (%)**
Recruitment source		
Main specialist paediatric hospital (research site)	39 (39.4)	14 (48.3)
Other NHS hospital sites (PIC)	14 (14.1)	7 (24.1)
Specialist teacher/local practitioner	31 (31.3)	5 (17.2)
Self-referral	15 (15.2)	3 (10.4)
Male	55	16
Female	44	13
North East England	2 (2)	0
North West England	2 (2)	1 (3.5)
Yorkshire and Humber	6 (6.1)	1 (3.5)
East Midlands	8 8.1	5 17.2
West Midlands	11 (11.1)	2 (6.9)
East of England	18 (18.2)	1 (3.5)
Greater London	20 (20.2)	9 (31.0)
South East England	16 (16.2)	5 (17.2)
South West England	9 (9.1)	3 (10.3)
Rest of UK (Scotland, Wales, Northern Ireland)	7(7.1)	0
Address unknown	0 (0)	2 (6.9)

Subdivisions of the United Kingdom of Great Britain and Northern Ireland from the Nomenclature of Territorial Units for Statistics (NUTS); spilt into 'first level' regions (Office for National Statistics UK).

Table 4. Parental and family demographics of infants with CDPVS

Parent/ family variable	**XXXX cohort (n=90)**	**UK population census (%)**
Census Mapped categories	**n (%)**	
Level of maternal education		
No qualifications / level 1+2 Secondary school (no A levels)	21 (23.3)	55.1
Level 3 A levels/final year examinations/ some higher education	20 (22.2)	12.0
Level 4 University graduate/ higher degree/ professional postgraduate	45 (50.0)	26.7
Missing data	4 (4.4)	
BME*		
White	66 (73.3)	87.1
Mixed/multiple ethnic groups	3 (3.3)	2.0

Asian/ Asian British	7 (7.8)	6.9
Black/ African/ Caribbean/ Black British	4 (4.4)	3.0
Missing data	10 (11.1)	

*BME categories according to the recommended framework: Harmonised concepts and questions for social data sources primary standards for presentations of UK outputs on ethnic groups .

Figure 1 Relationship between vision level (NDS) and SMU DQs (sighted norms) Total sample (n=90)