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ORIGINAL ARTICLE

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Aims: To determine the prevalence of ophthalmic impairments in very preterm compared with term infants, the relation between impairments and cerebral ultrasound appearances and retinopathy, and the correlation with visual perception and motor and cognitive measures.
Subjects: 279 children at 7 years of age born before 32 weeks gestation within Liverpool during 1991–92 and attending mainstream schools, and 210 term controls.
Methods: Visual acuity was assessed by Snellen chart, and strabismus by the cover test. Stereopsis was determined using the TNO random dot test, and contrast sensitivity using the Cambridge low contrast gratings. Visual and motor abilities were assessed using the Developmental test of motor integration (VMI) and the Movement ABC. Intelligence was measured with the Wechsler intelligence scale for children UK. Perinatal cranial ultrasound and retinopathy data were extracted from clinical records.
Results: Children born preterm were significantly more likely to wear glasses, to have poor visual acuity, reduced stereopsis, and strabismus than term controls, but they showed no significant decrease in contrast sensitivity. Ophthalmic impairments were significantly related to poorer scores on the VMI, Movement ABC, and Wechsler IQ tests, but were not significantly related to neonatal cranial ultrasound appearances. Stage 3 retinopathy was related to poorer subsequent acuity.
Conclusions: Children born very preterm and without major neurodevelopmental sequelae have an increased prevalence of ophthalmic impairments at primary school age which are associated with visual perceptional, motor, and cognitive defects. The cause may be a generalised abnormality of cortical development rather than perinatally acquired focal lesions of the brain.

Although many studies of children born preterm have shown them to be at higher risk of ophthalmic impairments, most of these studies predate recent improvements in perinatal and neonatal care.[1–3] It is likely that some of these impairments may now be being prevented, although increased survival of the most immature infants may increase the number of such children at risk. Three recent population based studies suggest that ophthalmic impairments remain common in very low birthweight infants.[4–6] Ophthalmic impairments are often associated with other cognitive and motor impairments, and contribute considerably to learning difficulties during school years.[1] In the most immature infants, retinopathy of prematurity (ROP) is a major associate of subsequent ophthalmic impairment, whether treated or not.[4–8] The incidence of severe ROP may be decreasing, possibly because of screening programmes and early treatment with cryotherapy or laser therapy, or because of improved management of respiratory distress syndrome.[9 10] This, however, has been disputed.[11] In some reports, damage to visual pathways by lesions such as periventricular leucomalacia is considered an even more important cause of impairment in the very preterm.[12 13] Both conditions may lead to blindness or severe visual impairment, although fortunately most visual impairment in the preterm is less severe. Reduced visual acuity, strabismus, and refractive errors are very common, and may occur in up to a third of such children.[14–17] More subtle yet important impairments reported include abnormalities of stereopsis, colour vision, and contrast sensitivity. Many children with the latter problems may be thought to have otherwise normal vision.

This study aims to examine a geographically defined population of very preterm infants for visual function at 7 years of age at normal school and to compare them with term controls. The relation of ophthalmic defects to earlier cerebral ultrasound scan appearances and evidence for ROP is explored, and correlations between visual defects and visual perception, motor, and cognitive problems defined.

PARTICIPANTS AND METHODS

Participants

All infants born before 32 completed weeks in 1991–92 in the eight hospitals within the Liverpool postal districts were ascertained. Those who died before discharge from hospital or whose mothers were not resident within a Liverpool postal district at the time of birth were excluded.

Initial contact was made with the family doctor through the child's hospital paediatrician to ascertain current health status and school placement. The parents of those children who were alive and attending mainstream schools were then approached to seek consent for their child to take part in the study. The individual children's schools were then contacted to arrange assessment visits, and to request that the class teacher choose the child of same sex and first language in the class whose birthday was closest to that of the index child. The parents of that control child were then approached with information about the study, and consent for their child to participate was sought. Most children were tested at their schools, although a few were tested at the Institute of Child Health, Royal Liverpool Children's Hospital, at their parents

Abbreviations: IQ, intelligence quotient; Movement ABC, Movement assessment battery for children; PVH, periventricular haemorrhage; PVL, periventricular leucomalacia; ROP, retinopathy of prematurity; VMI, Developmental test of visual-motor integration

request. The study protocol was approved by the local research ethics committee.

Vision tests

Visual acuity was assessed using a standard Snellen chart. Monocular visual acuity was assessed for each eye at a distance of 6 m. A score of 6/9–6/6 is considered normal.[18] The Snellen chart was used because of its ease of use in the school situation, although better and more precise tests are now available. It was noted if children wore spectacles. A cover test was performed to detect the presence of strabismus. If it was present, it was noted to be latent or manifest, the laterality observed and whether it was alternating. Stereopsis was determined using the TNO random dot test.[19] This has been designed as a screening tool for school age children. The test plates viewed through red-green spectacles can identify retinal disparities ranging between 15 and 480 seconds of arc; 120 seconds of arc is recommended as a pass/fail criterion by the test authors. Contrast sensitivity was assessed using the Cambridge low contrast gratings.[20] This is a simple and quick screening test, and is suitable for use with subjects with normal Snellen visual acuity. The gratings on the test measure contrast sensitivity at only one spatial frequency of 4 cycles/degree. No normative data are published for this test. Children with an acuity of worse than 6/9 were excluded from this test. Scores of 120 or less were considered abnormal.

All the visual tests were applied by a single observer (L F-H).

Other test instruments used

Integration of visual and motor abilities was assessed using the Developmental test of visual-motor integration (VMI).[21] It consists of 27 geometric forms which increase in complexity and are in a developmental sequence. There is a one point scoring system for each shape copied by the child. Scores are standardised for age. Standard scores have a mean of 100 and a standard deviation of 15.

Fine and gross motor skills were assessed using age band 2 of the Movement assessment battery for children (Movement ABC).[22] The test comprises eight items, divided into four subsections: manual dexterity, ball skills, and static and dynamic balance. The scoring system for each item is from 0 to 5 ranging from no impairment to severe impairment. The scores for each item are added and converted into centiles. A score between the 5th and 15th centile for age is considered ''borderline'' impairment, and at or below the 5th centile ''definitely impaired''.

General intelligence was measured using the Wechsler intelligence scale for children UK (WISC III UK).[23] Total, verbal, and performance scores were calculated.

The occipitofrontal head circumference was measured in a standard manner.

Perinatal data

Perinatal data were abstracted from the clinical case records at the eight hospitals using a standard proforma. The results of cranial ultrasound examinations were recorded, and the most extensive degree of periventricular haemorrhage (PVH) and periventricular leucomalacia (PVL) observed was recorded. Infants weighing less than 1500 g were routinely screened in the neonatal period and later for ROP according to established national guidelines.[24] The most extensive ROP observed defined by zone and stage was recorded for each eye.

Statistical analysis of data was carried out using parametric or non-parametric tests depending on the distribution of the data.

RESULTS

Of a potential cohort of 382 preterm children identified, 33 had moved out of the area or could not be traced, six were traced but failed to attend appointments for testing, 18 had died, 29 were attending special schools, and 16 parents refused permission for their children to be tested. In addition to these 280 children, 210 term controls were also recruited. In 70 cases, a control was not obtained, or the parents of the control selected would not agree to testing. Time constraints at school meant that a few children did not complete all the tests. The index children comprised 151 (53.9%) boys and 129 (46.1%) girls. The term controls comprised 112 (53.3%) boys and 98 (46.7%) girls. The mean gestational age for the index group was 29.8 (range 23–32) weeks and the mean birth weight 1467 (range 512–2860) g. Nearly a quarter (21.4%) were $\leqslant$ 28 weeks gestation, and 3.6% $\leqslant$ 24 weeks. Half (50.4%) weighed $<$ 1500 g at birth and 14.6% $\leqslant$ 1000 g. There were 215 singleton births, 56 twins, and nine triplets. The mean age at testing was 89.8 (range 82–101) months for the index children and 89.9 (range 72–107) months for the controls.

All but one of the preterm children (279) and all 210 controls received full visual screening. One preterm child could not complete the visual tests because of an acute eye infection. Of the 143 preterm children who had weighed less than 1500 g at birth (very low birthweight), 115 (80.4%) had been screened for ROP.

Visual acuity

Thirty six (12.8%) of the preterm and nine (4.3%) of the term control children wore spectacles ($p = 0.002$). Table 1 shows Snellen visual acuity. Significantly poorer acuities were seen for either eye in the preterm children ($p = 0.007$ left, $p = 0.002$ right). Eighteen (6.5%) of preterm children had a visual acuity at 6 m of less than 6/9 in one or both eyes (14 left, 9 right). Three term children had poor acuity (two left, two right; $p = 0.01$).

Strabismus

Strabismus was detected in 38 (13.6%) preterm and three (1.4%) term control children ($p < 0.001$). Strabismus was manifest in 18 preterm and one control child. Latent strabismus was found in 20 preterm and two term children.

Stereopsis

Using 120 seconds of arc on the TNO as a pass/fail criterion, 115 (41%) of preterm and 26 (12.4%) term control children failed the test. Absent stereopsis was seen in 46 (16.5%) preterm and eight (3.8%) term control children ($p < 0.001$).

Contrast sensitivity

The median contrast sensitivity score was significantly lower at 190 and 210 for the left and right eye respectively for the

Table 1 Distribution of visual acuity (Snellen) by preterm and term groups and eye

	Left		Right	
Acuity	Preterm	Control	Preterm	Control
6/6	243	198	253	205
6/9	22	10	16	3
6/12	5	1	3	1
6/18	2	1	3	1
6/24	4		2	
6/36	3		1	
6/60			1	
Total	279	210	279	210

Significantly poorer visual acuity in the left or right eye in preterm infants ($p = 0.007$, $p = 0.002$ respectively; Mann-Whitney).

Table 2 Relation between visual impairments and visual perception, intelligence, and motor impairment

	VMI	Total IQ	Verbal IQ	Performance IQ	Movement ABC
Acuity					
⩾6/9	92 (85–97)	91 (80–99)	92 (84–102)	88 (78–99)	8 (3–14.5)
<6/9	85 (79–92)	82 (67–92)	91 (77–99)	74 (64–85)	17 (10–35)
	p = 0.019	p = 0.009	p = 0.183	p = 0.001	p<0.001
Normal	92 (85–97)	91 (80–99)	92 (78–99)	88 (78–99)	8 (3–14.5)
Strabismus	87 (81–95)	86 (75–98)	91 (79–102)	82 (67–97)	17 (7–32.5)
	p = 0.019	p = 0.145	p = 0.456	p = 0.079	p<0.001
Stereopsis (seconds of arc)					
⩾120	91 (84–96)	86 (78–98)	91 (82–102)	85 (76–97)	9 (4.4–16)
<120	94 (87–99)	94 (84–102)	95 (88–103)	95 (82–104)	6.5 (1.6–12)
	p = 0.010	p = 0.004	p = 0.052	p = 0.001	p = 0.022
Contrast sensitivity					
⩾150	92 (85–97)	91 (80–99)	92 (84–102)	88 (78–99)	8 (3–14.5)
<150	87 (82–97)	83 (77–96)	91 (81–100)	78 (69–90)	19 (10–28)
	p = 0.229	p = 0.048	p = 0.445	p = 0.008	p<0.001

Values are median (interquartile range).
IQ, Intelligence quotient; Movement ABC, Movement assessment battery for children; VMI, Developmental test of visual-motor integration

preterm than for either eye in the term controls (both median score 250, $p < 0.001$). Using a score of < 150 to represent significant impairment, 24 (8.6%) and 13 (4.6%) preterm children were impaired for their left and right eyes respectively, compared with nine (4.2%) and 11 (5.2%) for the term control children. These differences were not significant.

When the frequency of all ophthalmic impairments were compared between preterm children with a birth weight of greater than 1500 g and those of lower birth weight, no significant differences were found.

Relation between ophthalmic impairments and other functions

Significant differences in visual perception, motor impairment, and intelligence were seen between preterm children with and without ophthalmic impairments (table 2). Visual perception was significantly poorer in children with poor acuity, stereopsis, or strabismus. Overall intelligence was lower in children with poorer contrast sensitivity, stereopsis, or acuity, but this was due to poorer performance intelligence quotient (IQ), there being no significant differences in verbal IQ. Motor impairment was seen more often in children with poor acuity, stereopsis, contrast sensitivity, and strabismus.

Neonatal cranial ultrasound findings and visual impairments

Periventricular haemorrhage (PVH) was evident as subependymal haemorrhage in 11 (3.9%), intraventricular haemorrhage in 17 (6.1%), and parenchymal haemorrhage in three (1.1%). Cystic periventricular leucomalacia (PVL) was noted in three (1.1%). Grade of PVH was significantly related to the stage of retinopathy in those infants who had been screened in the neonatal period ($\chi^2 = 20.8$, $p < 0.013$). Strabismus, poor visual acuity, absent stereopsis, and low contrast sensitivity were unrelated to the maximum extent of PVH or PVL determined on neonatal cranial ultrasound scans.

Retinopathy of prematurity

Of the 115 preterm infants weighing less than 1500 g who were screened for ROP, 31 (27%) had stage 1, 20 (17.4%) had stage 2, and eight (7%) had stage 3 disease. No infants had plus disease or required treatment in this cohort. Of the 59 infants with retinopathy, the disease was present in zone 2 in 42 (71%) and zone 3 in 17 (29%) and occupied a median of 4 (interquartile range 3–7) clock hours. Stage of retinopathy was significantly related to gestation ($\chi^2 = 55$, $p < 0.001$). Stage of retinopathy was also significantly related to the wearing of glasses (χ^2 for trend 6.7, $p = 0.01$).

Moderate retinopathy (stage 3) was associated with significantly poorer scores on the Movement ABC and total and verbal IQ, but these differences were of borderline significance after standardising for gestational age (table 3). Moderate retinopathy was significantly associated with impaired acuity, but not lack of stereopsis, strabismus, or reduced contrast sensitivity in this cohort (table 4).

Occipitofrontal head circumference

The preterm group had a mean (SD) occipitofrontal head circumference of 51.5 (1.9) cm compared with 52.5 (1.6) cm for the term controls ($p < 0.001$). Significant correlations between occipitofrontal head circumference and visual,

Table 3 Relation between stage of retinopathy and visual perception and motor and cognitive abilities

Retinopathy stage	VMI	Movement ABC	Vocal IQ	Performance IQ	Total IQ
0, 1, 2	89 (9.9)	7 (3–17.5)	90 (13.0)	85 (15.9)	86 (14.3)
3	85 (15.4)	24.3 (5.6–33.8)	76 (14.8)	73 (15.3)	72 (13.9)
p Value	0.288	0.035	0.007	0.061	0.014
p Value*	0.746	0.053	0.046	0.386	0.110

Values are mean (SD) or median (interquartile range).
*Controlled for gestational age.

Table 4 Relation between stage of retinopathy and visual outcomes at 7 years of age

	Stage 0, 1 or 2	Stage 3	p Value
Strabismus	14	3	
No strabismus	94	5	0.092
Contrast sensitivity			
<150	6	2	
⩾150	102	8	0.095
Stereopsis			
<120	42	5	
⩾120	66	3	0.260
Acuity			
Left eye	6/6 (6/6–6/36)	6/6 (6/6–36)	0.380
Right eye	6/6 (6/6–6/60)	6/6 (6/6–6/36)	0.012

Acuity measured using the Snellen chart. Values are median (range).

motor, and cognitive outcomes were found for all children and the preterm group alone (table 5).

DISCUSSION

Poorer visual function was observed in the preterm infants than controls on all measures used except for contrast sensitivity. Three times as many preterm children wore glasses, three to four times as many had poor visual acuity or stereopsis, and nearly 10 times as many had strabismus.

Comparison of overall visual defects with other studies is problematic because of differences in the measures used and selection criteria. Previous estimates have been between 15% and 79% for abnormalities detected by standard visual screening.[1 4–6 25–27] It is easier to compare individual measures. Monocular visual acuity was poorer than 6/9 in 6.5% in either or both eyes in this study compared with 17% in a hospital based study on very low birthweight infants,[1] 37% in a cohort of children at 5 years born at less than 30 weeks gestation,[14] and 10.5% and 9.5% in studies of very low birthweight infants in which binocular acuity only was tested.[26] Geographical studies published recently have used more sensitive measures of acuity, but have reported poor acuity in similar proportions of their study cohorts.[4–6] Some 12.8% of the children in this study wore glasses for myopia or hypermetropia compared with 10–27%, and higher stages of ROP were associated with a greater likelihood of wearing glasses as previously reported.[4–6 8] Strabismus was present in 13.6%. Other studies have reported rates of 9.5–25%, with a positive association with ROP and PVH and PVL.[1 3–6 12 15 26–28] This association was not seen in this cohort probably because children with major disability were excluded.

More subtle tests of visual function such as contrast sensitivity and stereopsis showed higher rates of abnormalities in the preterm group as previously described.[7 29] A contrast sensitivity < 150 in one or both eyes was found in 9.7%, but it is difficult to compare this finding with other studies because of differences in measurement technique. Stereopsis was impaired (< 120 seconds of arc) in 43.3% and absent in 17.4% of the preterm group. This is similar to previous findings.[1 3 29]

The rates of ophthalmic deficits in this study are lower than in some earlier ones, although these differences are probably due to cohort selection. This cohort was selected by gestation and geographical area rather than by hospital, and may contain fewer growth restricted infants. Recent developments in neonatal management such as the extensive use of antenatal steroid prophylaxis and postnatal surfactant may have reduced the severity of disorders such as PVH and retinopathy, which would impact on later visual development. More importantly, this cohort excludes children who are not attending mainstream school, including all those with major disabilities such as cerebral palsy which are often associated with strabismus. On the other hand, survival of infants of 26 weeks and less has become much more common, and these children are likely to have a poorer prognosis. Comparison of infants with birth weights of above and below 1500 g showed no significant differences in visual outcomes, despite the significantly greater risk for PVH and ROP in the smaller babies. The actual rate of stages of ROP in those over 1500 g is unknown, however, as they were not screened. In those screened for retinopathy, the stage of ROP did not appear to relate to developmental outcomes when gestational age was allowed for. Neither did retinopathy appear to be significantly related to visual outcomes except for acuity. This may be because there were no severe cases of ROP in the cohort, or because modern screening and treatment programmes have reduced the risk of ROP affecting later vision. Previous studies have emphasised that it is mainly the severest grades of ROP involving zones 1 and 2 that affect later vision.[8]

It is of particular interest to know if the visual defects observed are likely to be related to poor school performance. In the preterm group, visual outcomes were significantly related to measures of intelligence, minor motor disability, and visual perception, with the exception of verbal IQ (table 2). The strongest associations were between visual outcomes and motor impairment as measured by the Movement ABC and performance IQ. Such associations have been described before and thought to be due to either a common neurological insult such as PVL or the direct effect of the visual defect on functional motor abilities. Ultrasound evidence of PVH and PVL was not associated with adverse visual outcomes in this cohort. This may have been because of the relatively low incidence of PVH/PVL seen because of exclusion of children with major disabilities, or because the causative lesion cannot be identified by neonatal cranial ultrasound scanning. The association of poor acuity and low contrast sensitivity with minor motor impairment would suggest that a diffuse cortical lesion such as defective myelination of the cerebrum may be responsible. Longitudinal magnetic resonance imaging studies in the preterm have shown that this does occur in preterm infants as they mature, and is associated with a smaller brain.[30 31] The preterm group had significantly smaller brains at age 7 years than controls, and brain size correlated with a wide range of visual, motor, and cognitive outcomes (table 5). This would suggest that in common with IQ and minor motor impairment, visual disabilities in the preterm, particularly subtle

Table 5 Correlations of occipitofrontal head circumference at 7 years of age with visual, motor, and cognitive outcomes

	Preterm (n = 279)		All (n = 489)	
	R value	p Value	*R* value	p Value
Strabismus	−0.116	0.054	−0.142	0.002
Acuity				
Left	−0.106	0.076	−0.113	0.013
Right	−0.116	0.052	−0.104	0.021
Contrast sensitivity				
Left	0.183	0.002	0.160	0.001
Right	0.256	0.001	0.198	0.001
Stereopsis	−0.108	0.073	−0.177	0.001
VMI	0.217	0.001	0.249	0.001
Movement ABC	−0.200	0.001	−0.248	0.001
Vocal IQ	0.251	0.001	0.274	0.001
Performance IQ	0.226	0.001	0.186	0.001
Total IQ	0.277	0.001	0.264	0.001

VMI, Developmental test of visual-motor integration; IQ, intelligence quotient.

ones such as impaired stereopsis and contrast sensitivity, in the absence of major disability, relate to poorer postnatal brain growth rather than ROP and PVH/PVL.

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