Ophthalmological follow up of preterm infants: a population based, prospective study of visual acuity and strabismus

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Abstract

***Background/aims*—Prematurely born infants are known to have an increased rate of ophthalmological morbidity. The aim of the present study was to investigate visual acuity and ocular alignment in a population of preterm infants in a geographical area, in infants with and without retinopathy of prematurity (ROP).**

***Methods*—A prospective population based study of ophthalmological status of preterm infants with a birth weight of 1500 g or less was performed during 3.5 years, with examinations at 6, 18, 30, and 42 months of corrected age. Visual acuity was tested using linear optotypes. Multiple regression analyses were used to analyse independent risk factors for poor vision and strabismus.**

***Results*—Poor vision (<0.3) was detected in 2.5% (6/237) of the children. Of these, only two (0.8%) had a severe visual impairment (<0.1). Strabismus occurred in 13.5% (31/229). Children with cryotreated ROP and neurological complications ran the highest risk of poor vision and strabismus, according to multiple regression analysis. Among children *without* a history of ROP or neurological complications, 34% had a visual acuity <0.7 and 5.9% had strabismus, compared with 61% and 22%, respectively, among the children *with* ROP or neurological complications.**

***Conclusions*—The overall incidence of subnormal vision and strabismus in children born prematurely was higher than in a full term population of the same age. On the basis of this study, follow up of all preterm infants screened for ROP is recommended and general guidelines are suggested.**

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Children born prematurely are reported to have an increased incidence of visual impairment, because of retinopathy of prematurity (ROP), but also because of perinatal lesions in the brain.[1–13] A recent study of incidence of visual impairment in Nordic children (visual acuity <0.3—that is, approximately <6/18) revealed 11.5% (35/304) of them as having been born preterm, which suggests that premature birth may have negative effects on visual function.[14] An increased incidence of strabismus has also been reported in children born prematurely, regardless of the presence of ROP.[1 3–7 15–19]

This study presents the results of examinations of visual acuity (VA) and ocular alignment from a 3.5 year follow up of a population of prematurely born children. The children came from a prospective study on the acute phase of ROP in a defined population of prematures in Stockholm, Sweden.[20] Detailed findings on refraction in these children have been presented elsewhere.[21] We aim to define guidelines for follow up of this increasing group of patients in need of specialised eye care.

Material and methods

The original prospective ROP study began in September 1988 and was concluded in October 1990. It included 260 prematurely born infants with a birth weight of 1500 g or less of whom 40% had suffered from ROP and 11% had been treated with cryopexy at a prethreshold stage[20]—that is, at a slightly earlier stage than advocated by the American Multicenter Study.[22]

In the present study, ophthalmological and orthoptic examinations were performed by experienced paediatric ophthalmologists and orthoptists at 6, 18, 30, and 42 months of corrected age—that is, the age calculated for birth at term. Cycloplegic retinoscopies were performed at the 6 and 30 month visits. Correcting glasses were prescribed, usually at 30 months of corrected age, when more than +3 D hypermetropia or more than −1 D myopia and/or more than −1 to −1.5 D of astigmatism (depending on the affected meridian) was found. Ocular alignment and stereopsis was tested at every visit. Eye motility was examined and cover test was performed. Stereopsis was assessed with Lang's test. The fundus was evaluated, usually at the 30 month retinoscopy, using a modification of the macular scoring system described in the American Multicenter Study[23]: score 3 = posterior retinal folds, retinal detachments, retrolental mass, score 2 = macular pigment epithelial scarring, score 1 = macular heterotopia, and score 0 = clinically normal macula.

From the original group of 260 infants, which has been described in detail in recent papers[20 21] seven children had died before 6 months of age and four were excluded because of ophthalmological or general diseases not related to prematurity. Of the remaining 249 infants, 227 came for ophthalmological follow up examinations during 3.5 years, resulting in a drop out frequency of 8.8% (22/249).

The present study mainly analyses visual acuity (VA) and strabismus. The best corrected

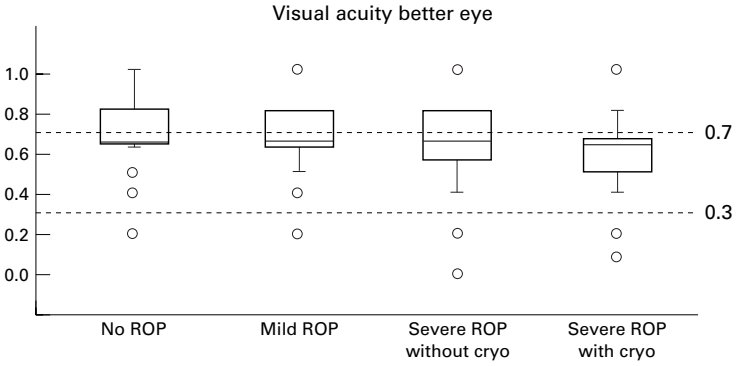

Figure 1 Visual acuity of the better eyes with respect to ROP stages (box plot diagram with median values and 25% and 75% percentiles).

monocular VA was assessed at the 42 month visit (mean age 44.8 months, range 36–54, SD 3.4) with linear optotypes, such as the HVOT[24] or LH[25] tests. Children who had not used their prescribed correction for at least 3 months before acuity testing were excluded from the VA analyses (two non-ROP affected children). If the child was not able to take part in the tests with linear optotypes, the "preferential looking" test with acuity cards was used (five children) and the results were converted from grating acuity to linear acuity. If neither of the above tests had been possible, the visual behaviour or fixation pattern was assessed (one mentally retarded child, with apparently normal visual behaviour, who was not included in the statistical analyses).

Thus, of the 227 children in whom VA was assessed at 3.5 years, 224 (227 minus the two children without glasses and the mentally retarded child who could not take part in a proper assessment) were included in the analyses of VA. However, another 13 children, who had dropped out after the first retinoscopy at 6 months, were also included in the analyses of VA. Their acuities were obtained from child healthcare centres, where all Swedish children are carefully tested monocularly with linear optotypes (see tests above) by specially trained nurses and orthoptists. One of these 13 had suffered from ROP stage 1. At the retinoscopy performed at 6 months of corrected age, most infants (11) had been found to be slightly hypermetropic (0 to +3 D), while one child had been + 3.5 D hypermetropic and one −1 D myopic. At 4 years of age, none of them was reported to have a VA below 0.65.

In the statistical analyses of VA altogether 237 children (224 plus 13) were thus included. The results are presented with regard to better and worse eyes as well as right and left eyes. For ease of reading the following grading of VA is used: "poor vision", VA <0.3 (approximately 6/18 Snellen equivalents), and "good vision", VA ≥0.7 (approximately 6/8.5).

Intraventricular haemorrhage (IVH) in the neonatal period[26] had been diagnosed in 32 children. An additional eight children were found to have obvious neurological sequelae such as cerebral palsy, epilepsy, or mental retardation. Thus, 40 children in the present study had neurological complications. Thirty six of them were followed throughout the complete study programme and were included in the analyses of VA (36/237, 15%).

Ocular alignment and stereopsis were analysed in 229 children. Apart from the 227 infants examined as scheduled, a further two drop outs were included. These two were both neurologically handicapped and had an early onset of strabismus before they dropped out. No children seen at the child healthcare centres were included in these analyses, since VA is the only reliable factor examined there.

STATISTICAL METHODS

The χ^2 test and Fisher's exact test were used to compare variables, measured on a nominal scale, and the paired *t* test and sign test for within group comparisons. Correlations were calculated with Pearson's product moment correlation coefficient.

Associations between various factors and degree of ROP, gestational age at birth, and birth weight were also analysed with frequency tables.

Stepwise regression analyses were performed to evaluate the effect of various risk factors on the VA. Stepwise logistic regression analyses were performed to determine the main factors predicting strabismus.

Table 1 Visual acuity of the better eye

ROP	*<0.1*	*0.1–0.29*	*0.3–0.49*	*0.5–0.69*	*≥0.7*	*Total*
(A) Relation to stage of ROP						
No	0 (0%)	1 (0.7%)	1 (0.7%)	50 (35%)	91 (63.6%)	143 (100%)
Mild	0 (0%)	1 (2.2%)	2 (4.3%)	23 (50%)	20 (43.5%)	46 (100%)
Severe without cryo	1 (4.2%)	1 (4.2%)	2 (8.3%)	9 (37.5%)	11 (45.8%)	24 (100%)
Severe with cryo	1 (4.2%)	1 (4.2%)	2 (8.3%)	16 (66.7%)	4 (16.6%)	24 (100%)
Total	2 (0.8%)	4 (1.7%)	7 (2.9%)	98 (41.4%)	126 (53.2%)	237 (100%)
(B) Relation to gestational age at birth (weeks)						
24–26	1 (3.3%)	0 (0%)	2 (6.7%)	15 (50%)	12 (40%)	30 (100%)
27–29	1 (0.9%)	3 (2.7%)	4 (3.6%)	49 (43.7%)	55 (49.1%)	112 (100%)
30–32	0 (0%)	1 (1.3%)	1 (1.3%)	28 (36.9%)	46 (60.5%)	76 (100%)
33–35	0 (0%)	0 (0%)	0 (0%)	6 (31.6%)	13 (68.4%)	19 (100%)
Total	2 (0.8%)	4 (1.7%)	7 (2.9%)	98 (41.4%)	126 (53.2%)	237 (100%)
(C) Relation to birth weight (g)						
≤750	1 (10%)	0 (0%)	1 (10%)	6 (60%)	2 (20%)	10 (100%)
751–1000	0 (0%)	1 (1.9%)	1 (1.9%)	21 (38.8%)	31 (57.4%)	54 (100%)
>1000	1 (0.6%)	3 (1.7%)	5 (2.9%)	71 (41%)	93 (53.8%)	173 (100%)
Total	2 (0.8%)	4 (1.7%)	7 (2.9%)	98 (41.4%)	126 (53.2%)	237 (100%)

Table 2 Stepwise, multiple regression analysis of the visual acuity of the better eye. The constant illustrates a predictive value of a visual acuity of 0.77 in a child without ROP or neurological complications. The acuity will be reduced to 0.68 if neurological complications are present and to 0.52 if the child also has ROP and is given cryotherapy

Variable	*Coefficient*	*Standard error of coefficient*
Constant	0.7688	
Neurological sequelae	−0.0861	0.0306
ROP mild	−0.0603	0.0284
ROP severe without cryo	−0.1016	0.0367
ROP severe with cryo	−0.1583	0.0371

R^2 = 12%.

Results

VISUAL ACUITY (VA)

Mean value of VA

The mean VA of the right and left eyes were 0.70 (SD 0.20) in both eyes in the 237 children.

Relation of VA to gestational age and birth weight—A correlation between low VA of the right and left eyes, respectively, and low gestational age was found (r=0.20, p<0.01), but none to low birth weight.

Relation of VA to degree of ROP—There was a significant difference between the mean VA of eyes with ROP when compared to eyes without ROP (p<0.001), the difference being most marked when cryotreated eyes were compared with all remaining untreated eyes in the study (including untreated eyes with ROP). The mean VA was 0.50 (SD 0.24) in cryotreated right eyes (23) and 0.72 (0.18) in all untreated right eyes (214). In left eyes, the corresponding VA were 0.56 (0.24) in cryotreated eyes (24) and 0.71 (0.19) in untreated eyes (213) (p<0.0001).

Visual acuity of the better eye

The mean VA of all better eyes was 0.72 (0.18).

Relation of VA of the better eye to gestational age and birth weight (Tables 1B, C)—A correlation between best VA and gestational age at birth was found (r=0.21, p<0.001), but none to birth weight.

Relation of VA of the better eye to degree of ROP (Fig 1, Table 1A)—There was a significant difference between the mean VA of better eyes with ROP (0.65 (SD 0.20)) when compared with eyes without ROP (0.76 (0.15)) (p<0.001). This difference was most pronounced when cryotreated eyes (24 eyes) (mean value of VA 0.59 (0.21)) were compared with all untreated eyes (213 eyes) (mean value of VA 0.73 (0.17)) (p<0.001).

Figure 1 and Table 1 illustrate the distribution of VA in the better eyes in relation to various degrees of ROP. As seen in Table 1A, poor vision (<0.3) was commonest in eyes with severe ROP (8%), while good vision (≥0.7) was commonest in eyes without ROP (64%).

Altogether 126 of the 237 children (53%) had good VA—that is, ≥0.7 in their better eyes (Table 1). Six children (2.5%) had poor VA (<0.3). Only two children (0.8%) in the entire study group had a best corrected VA of <0.1. One boy had become blind (no light perception) because of bilateral retinal detachments. Another boy, cryotreated for severe ROP, had VAs of 0.08 and light perception (p), respectively (see also Table 4, cases 150 and 194).

The effect of risk factors for poor VA of the better eye was evaluated with multiple regression analysis. These factors included gestational age at birth, birth weight, intraventricular haemorrhage (IVH) and major neurological sequelae, degree of ROP, cryotherapy, and spherical equivalent. Neurological complications, such as IVH and obvious neurological sequelae, and degree of ROP—particularly cryotreated ROP—proved to be important factors affecting the visual acuity of the better eye (Table 2).

Visual acuity of the "worse" eye

The mean VA of the worse eyes was 0.67 (SD 0.21) in the 237 children.

Relation of VA of the worse eye to gestational age at birth and birth weight (Tables 3B, C)—The distributions of VA of the worse eye in relation to gestational age at birth and birth weight are presented in Table 3B and C. A correlation between VA of the worse eye and gestational age at birth was found (r=0.19, p<0.01), but none to birth weight.

Relation of VA of the worse eye to degree of ROP (Table 3A)—There was a significant difference between the mean VA of worse eyes with ROP (mean value of VA 0.6 (SD 0.24)) when compared with eyes without ROP (mean value of

Table 3 Visual acuity of the worse eye

ROP	*<0.1*	*0.1–0.29*	*0.3–0.49*	*0.5–0.69*	*≥0.7*	*Total*
(A) Relation to stage of ROP						
No	0 (0%)	2 (1.4%)	7 (4.9%)	53 (37.1%)	81 (56.6%)	143 (100%)
Mild	0 (0%)	2 (4.4%)	2 (4.4%)	23 (50%)	19 (41.2%)	46 (100%)
Severe without cryo	2 (8.3%)	1 (4.2%)	2 (8.3%)	9 (37.5%)	10 (41.7%)	24 (100%)
Severe with cryo	1 (4.2%)	5 (20.8%)	2 (8.3%)	13 (54.2%)	3 (12.5%)	24 (100%)
Total	3 (1.3%)	10 (4.2%)	13 (5.5%)	98 (41.3%)	113 (47.7%)	237 (100%)
(B) Relation to gestational age at birth (weeks)						
24–26	1 (3.3%)	4 (13.3%)	0 (0%)	13 (43.4%)	12 (40%)	30 (100%)
27–29	1 (0.9%)	4 (3.6%)	8 (7.1%)	51 (45.5%)	48 (42.9%)	112 (100%)
30–32	1 (1.3%)	2 (2.6%)	3 (4%)	29 (38.1%)	41 (54%)	76 (100%)
33–35	0 (0%)	0 (0%)	2 (10.5%)	5 (26.3%)	12 (63.2%)	19 (100%)
Total	3 (1.3%)	10 (4.2%)	13 (5.5%)	98 (41.3%)	113 (47.7%)	237 (100%)
(C) Relation to birth weight (g)						
≤750	1 (10%)	0 (0%)	1 (10%)	6 (60%)	2 (20%)	10 (100%)
751–1000	0 (0%)	4 (7.4%)	3 (5.6%)	19 (35.2%)	28 (51.8%)	54 (100%)
>1000	2 (1.1%)	6 (3.5%)	9 (5.2%)	73 (42.2%)	83 (48%)	173 (100%)
Total	3 (1.3%)	10 (4.2%)	13 (5.5%)	98 (41.3%)	113 (47.7%)	237 (100%)

Table 4 Visual acuity < 0.3 in right and/or left eye

Id no	Gestational age (weeks)	Birth weight (g)	Visual acuity		ROP stage		Cryo		Retina	Strabismus	Optic atrophy	IVH	Neuro	Func ambl	Refraction last retinoscopy		Comments
			Right	Left	Right	Left	Right	Left							Right eye	Left eye	
19	29	1210	0.1	0.2	3	3	+	+	Macular heterotopia right > left	+	–	–	–		−5= −1 cyl 0°	−8= −1 cyl 90°	
20	29	1085	0.4	0.25	3	3	–	–		–	–	–	–		+1.0	+1.0	Poor vision of unknown aetiology
21	30	1390	0.2	0.02	3	3	–	–		+	+	3	+		−1= −1.5 cyl 135°	−1.5= −2 cyl 45°	
63	26	1095	0.4	0.1	3	4	+	+		+	–	1	+	+	+2.0	+2.0	
93	30	1188	0.2	0.63	3	3	+	+	Macular heterotopia right	+	–	–	–		−1= −1 cyl 20°	−0.5= −0.5 0°	
146	26	810	0.16	0.4	4	3	+	+	Macular heterotopia right	+	–	–	–		−3= −1 cyl 100°	+1= −0.5 90°	
150	27	1048	0	0	5	5	Too late	Too late	Amotio bilat (op)	+	Not possible	–	–		Not possible	Not possible	
161	26	908	0.1	0.5	3	3	+	+		+	–	3	+	+	−4= −2 cyl 80°	+2	
162	27	858	0.2	0.2	1	1	–	–		–	–	1	+		+2.5= −1.5 cyl 90°	+2.5= −1.5 cyl 90°	Mental retard
172	30	1380	0.2	0.63	0	0	–	–		+	–	–	–	+	+2= −2 cyl 60°	+2= −0.5 cyl 90°	
194	24	675	0.08	p	4	4	+	+	Macular heterotopia left > right	+	–	–	–		−7= −1.5 cyl 20°	−8	
217	25	909	0.63	0.10	1	1	–	–		+	–	–	–	+	+1= −1 cyl 100°	−3= −2 cyl i 0°	
266	28	1185	0.2	0.2	0	0	–	–		+	–	4	+		+2= −1 cyl 45°	+2= −1 cyl 135°	

Id no = identification number; IVH = intraventricular haemorrhage; neuro = includes children with IVH and/or neurological sequelae, see definition; func ambl = functional amblyopia (strabismus and/or anisometropia); p = perception.

VA 0.72 (0.18)) ($p<0.001$). This difference was most pronounced when cryotreated eyes (mean value of VA 0.48 (0.26)) were compared with all untreated eyes (mean value of VA 0.70 (0.19)) ($p<0.001$).

The distribution of visual acuity of the worse eyes in relation to degree of ROP is presented in Table 3A. Poor vision (<0.3) was commonest in eyes with severe ROP (19%), whereas good vision (≥0.7) was commonest in eyes without ROP (57%).

Characteristics of children with poor visual acuity (<0.3) in either eye

The ophthalmological and medical data in 13 children with poor vision in one or both eyes are listed in Table 4. Six children (2.5%) had poor vision (<0.3) in both eyes. Poor vision was found in all stages of ROP and also in children without ROP. Among the seven untreated children, two had monocularly reduced vision secondary to functional amblyopia (anisometropia and strabismus) (cases 172 and 217), three were neurologically damaged (cases 21, 162, 266) (case 21 also had optic atrophy), and one child had visual impairment of unknown aetiology (case 20).

STRABISMUS

Strabismus was found in 31 of the 229 children in the study of ocular alignment (13.5%). The mean age of onset of strabismus was 19.1 months (range 3–46, SD 15.1). Twenty four children had esotropia (77.4%) and seven had exotropia (22.6%). The frequency of strabismus was 18.1% in children with ROP (17/94) and 10.4% in those without (14/135) (Table 5). In cryotreated children, strabismus was observed in 40% (10/25), compared with 10.3% in all untreated children (21/204) ($p<0.001$).

In children with neurological complications, strabismus occurred in 34% (13/38). Among the 191 children without neurological complications 9.4% (18) had developed strabismus. In these children without neurological complications, strabismus occurred in 15.3% if they had suffered from ROP (11/72), but in 5.9% if no ROP had been found (7/119) ($p<0.05$).

Independent risk factors for strabismus were evaluated with stepwise, logistic multiple regression analysis. These included different stages of ROP, neurological complications, such as IVH and/or neurological sequelae, heredity of strabismus, bilateral spherical refraction of more than +3 D and anisometropia. Neurological complications, anisometropia (≥1 D) at first retinoscopy and cryotreated ROP were found to be important risk factors for strabismus (Table 6). No regression analysis was performed on the results of the second retinoscopy, because most children had already developed strabismus.

Stereopsis (Lang's test) could be determined at a mean age of 20.2 months (range 4–49, SD 8.7). Stereopsis was recorded in 195 of the 229 children (85.2%). Two children could not give a reliable answer. Thirty two children lacked

Table 5 Incidence of strabismus in relation to severity of ROP and presence of neurological complications ("neuro") (Strabismus in total study group 13.5% (31/229))

	Strabismus		*Strabismus*
ROP	18% (17/94)	No ROP	10.4% (14/135)
Cryotreatment	40% (10/25)	No cryotreatment	10.3% (21/204)
"Neuro"	34% (13/38)	No "neuro"	9.4% (18/191)
"Neuro" and/or ROP	22% (24/110)	No "neuro" or ROP	5.9% (7/119)

stereopsis and 27 of them had manifest strabismus. Among the remaining five children, one had congenital nystagmus, none had known neurological complications, and none had poor vision (that is, <0.3).

MACULAR FINDINGS

The last fundus evaluation was performed in 229 children at a mean age of 35.6 months (range 18–67, SD 8.3). Nine of them (3.9%) had pathological maculae and had suffered from severe ROP. Of these, eight had been cryotreated. In the ninth child, stage 5 ROP had been diagnosed too late for cryotherapy and the vitreoretinal surgery was unsuccessful—that is, bilateral macular score 3 had developed. Of the remaining eight children with macular pathology, five had bilateral heterotopia (four had bilateral macular score 1 and one child had bilateral macular score 2) and three children had macular score 1 in one eye and score 0 in their other eye. The vision in the eyes with heterotopic maculae—that is, score 1, ranged from 0.1 to 0.65. The child with bilateral scarring of the maculae (score 2) had only light perception in one eye and a VA of 0.08 in the other one.

MISCELLANEOUS

Optic atrophy was seen in three of 229 children (1.3%), all of whom had suffered from IVH grade 3. One of these children had developed ROP stage 3, but not the criteria for cryotreatment, and another one had reached only ROP stage 2. The third child had no ROP.

Nystagmus was detected in 11 of 229 children (4.5%). Five of them had suffered from IVH. One showed pale discs. In 10 of the 11 children with nystagmus, severe ROP had been present. Seven of them had been cryotreated of whom four had poor vision (<0.3) in at least one eye, and one had undergone vitreoretinal surgery and had no light perception. The only child without ROP was diagnosed as having congenital idiopathic nystagmus with abnormal head posture. He also had anisometropia, with bilateral myopia and astigmatism, and a slight amblyopia in one eye. He had no strabismus.

Table 6 Stepwise logistic regression analysis of risk factors for strabismus

				95% CI of odds ratio	
Risk factor	*Log odds ratio (b)*	*Standard error of b*	*Odds ratio*	*Lower bound*	*Upper bound*
"Neuro"	1.582	0.453	4.86	1.99	11.9
Anisometropia	1.451	0.613	4.27	1.28	14.3
Cryotherapy	1.334	0.522	3.79	1.36	10.6
Constant	−2.715				

"Neuro" = includes children with IVH and/or neurological sequelae.

Discussion

The present prospective study deals with the long term effects of prematurity on development of visual acuity and strabismus in infants with a birth weight of 1500 g or less.[20] The analysis of refractive errors in this population has been presented in a previous paper.[21]

VISUAL ACUITY

Visual acuity was recorded in 237 of the study population of 249 (95.2%). Most children (97.5%) were tested with linear optotype charts, as in the American Multicenter Study.[12] In that study, 92% of the children returned for visual acuity testing at 3.5 years, but only 73% could be tested with optotypes. It cannot be ascertained whether the difference is due to more severe ROP in the American study, a higher frequency of neurological complications, or a combination of both. In the present study, five children, of whom four had neurological damage, were tested with "preferential looking" (PL).

We recommend the use of linear optotype charts for testing visual acuity in prematurely born children. Testing with single optotypes can overestimate acuity in these children. It has recently been reported that a pathological crowding phenomenon with poorer linear than single optotype acuity is found in preterm children with ischaemic cerebral lesions, particularly in those with periventricular leucomalacia.[13 27] This condition should be detected because it may cause difficulties in the everyday life of these children.

In any study of an ophthalmologically diseased paediatric population, many variables, including visual acuity, may be expected to deviate from a normal cohort. Thus, our finding that only 53% (126/237) of a population of prematures had "good" visual acuity (≥0.7) is low compared with 93.9 % of 4 year old children with similar "good" vision in an unselected Swedish population.[28] Although the children in the present study were compared with a 6 month older cohort in the study of a normal population,[28] the finding of only 53% with "good" vision at 42 months of age may reflect delayed visual maturation, but also ocular and neurological sequelae or a combination of both.

Only two children—that is, 0.8% (2/237), in the present study were found to be severely visually handicapped, one of whom was blind (no light perception). This low number of severe visual impairments accords with the results in the study by Gallo and Lennerstrand.[1] However, it contrasts with the higher numbers (1.4% to 3.2%) of visually handicapped reported in other population based studies on prematures.[2 7 8 11] Perhaps our better results can be explained by the more liberal indications for cryotreatment used in the present study compared with the American Multicenter Study. In Stockholm, cryotreatment was performed at an earlier stage of the disease, also at "prethreshold"—that is, when proliferations were present in at least 4 clock hours, even in the absence of "plus disease". Although our interpretation may be regarded

as biased, the results seem to warrant a discussion whether to perform cryotreatment in the "prethreshold" stage rather than at "threshold", as advocated by the American Multicenter Study.[22] In addition, Tasman has already questioned the high anatomical and functional failure rate after treatment at "threshold disease"[29] and recently Goble *et al*[30] have questioned the rationale for delaying cryotreatment until there is a 50% risk of blindness.

In the present study, severe reduction of visual acuity was independently associated with neurological complications and with severity of ROP. This finding supports the view that ROP may not be the only cause of impaired visual acuity in prematurely born children, but that neurological complications may have a considerable effect.[13 31 32] In our study population, these relations were also apparent in the six children with "poor" vision (<0.3) in their better eye (Table 4). In half of the children (cases 21, 162, 266) neurological lesions seemed to be the major cause and in the other half (cases 19, 150, 194), ROP was the obvious cause of visual impairment.

An important finding was that children born prematurely with neither ROP nor neurological complications also ran a higher risk of developing suboptimal vision. Among 128 of these children, 44 (34%) did not achieve "good vision" (0.7), as opposed to the 6% in a full term population[28] who may develop subnormal vision. This result is supported by several others.[33–35] The underlying mechanisms could only be surmised, as our present diagnostic methods are obviously insufficient. Minor or transient cerebral incidents may have induced malfunction of the visual pathways, the visual centra, and/or their associative areas. It has also been shown that slight retinal dysfunction of the outer and inner retina may persist in prematurely born children without severe ROP.[36 37] At present, it is not known whether the affected child may later compensate for this unexplained visual deficit. Further, it was found that in cases with macular pathology it was not possible to predict visual acuity from the appearance of the macula in the individual child. As shown in the present study, the visual acuity could range from 0.1 to 0.65 in cases of macular heterotopia, which accords with the findings of Reynolds *et al.*[38]

STRABISMUS

The incidence of strabismus at 3.5 years of age in the present study (13.5%) was much higher than reported in populations born at term (Gallo and Lennerstrand[1] 2.1%, Köhler and Stigmar[28] 1.6%). This result is in accordance with other follow up studies of prematurely born children.[1 3–7 15–19] Detailed comparisons of incidences in the various studies are extremely difficult, since the criteria for inclusion may vary, particularly with respect to neurological complications and their definitions.

As expected, the incidence of strabismus was highest in children with ROP, particularly in those given cryotherapy (40%), as well as in those with neurological complications (31%). The incidence of strabismus among children without ROP or neurological sequelae (5.9%) was also higher than in a normal population.[1 28] Undetected minor or transient cerebral incidents may have been the cause. Obviously, detailed studies of the brain in preterms would help to elucidate this matter further.

Esotropia was the dominating type (24/31, 77%) of strabismus, in accordance with the other studies of preterm children. In the present study, 70% of the strabismus seen at 3.5 years commenced before 30 months of corrected age, which ought to be taken into account in designing follow up programmes. Functional amblyopia (that is, amblyopia secondary to strabismus with or without anisometropia) occurred in 28% of the strabismic children and was probably detected and treated earlier because of their participation in this study.

Stereopsis was assessed with Lang's test. The wide range of ages at which stereopsis could first be evaluated (4–49 corrected months) emphasises the difficulty of interpreting this test in young children. The mean age at which stereopsis was determined (20.2 months) was considerably higher than in full terms, who are reported to develop stereopsis at 4–6 months.[39 40] However, as the children were only examined at certain predetermined intervals (6, 18, 30, and 42 months of corrected age) the onset is difficult to evaluate more exactly.

Stereopsis could not be recorded in 32 children. The majority (27) had manifest strabismus, one had congenital nystagmus, while four had no obvious explanation for the lack of stereopsis. Whether undetected subtle neurological lesions could be the reason remains an unanswered question.

NEUROLOGICAL LESIONS

In the present study, neurological complications, defined as "IVH and/or obvious neurological sequelae such as mental retardation, cerebral palsy and/or epilepsy", proved to be significant risk factors for impaired vision as well as for strabismus. Neurological lesions of the preterm brain, mainly lesions of a haemorrhagic and ischaemic nature, may affect visual functions in varying degrees.[13 27 32 41 42] Routinely scheduled neuroradiological examinations in the neonatal period and during follow up would obviously have been useful to distinguish between the effects of ROP and neurological sequelae on visual function and strabismus. Despite this shortcoming in our study, the possible effects of neurological lesions on strabismus and on the visual outcome in the prematurely born child must be recognised.

OPHTHALMOLOGICAL SCREENING AND FOLLOW UP

Use of a schedule for long term ophthalmological follow up of children born prematurely has not gained as much attention as screening for ROP in the neonatal period. Ideally, ophthalmological screening and follow up programmes for prematurely born children should be based on population studies. Socioeconomic factors, as well as the organisation of neonatal and general health care in a particular

area, may affect the incidence and course of ROP, the incidence of neurological lesions and also the facilities for follow up.

In a previous paper,[20] a screening programme was proposed for the eye care of ROP in the immediate neonatal period. We recommended that all infants with a gestational age of 32 weeks or less should be included in the programme as well as children with a birth weight of 1500 g or less, if there was any doubt about their gestational age.

The present study showed that increased ophthalmic morbidity is to be expected in a population of prematurely born children. Apart from the obvious ROP related complications, the prematures run an increased risk of visual impairment and strabismus. A very important finding in this study was that even premature infants who had not suffered from ROP were also at increased risk of developing subnormal vision and strabismus. A previous study revealed that this group of prematures also has an increased risk of myopia and anisometropia.[21] Therefore, *all* prematures in the neonatal screening programme for ROP should be included in a follow up programme as well.

The ophthalmological follow up programme must necessarily be limited to ophthalmological and general healthcare resources available in a given area. Based on the results of the present long term study of a prematurely born population, the following guidelines for the most beneficial timing of one to three available examinations are given:

If one examination will be performed (at about 12 months of corrected age)

This examination should include assessment of visual behaviour and ocular alignment, retinoscopy and fundus evaluation. If the retinoscopy is performed too early—that is, before 6 months of corrected age, there is a high risk of finding transient physiological myopia,[21 43] which necessitates a second, perhaps useless examination. Children with normal ophthalmological examinations—unless having a history of cryotreatment or neurological complications—should then be followed up in the general healthcare system, if that is available.

If two examinations will be performed (at 12 and at 24–30 months of corrected age)

At about 2 to 2.5 years, possible physiological myopia should have disappeared[44] and developmental astigmatism should have "settled". By this time, a major part of eventual strabismus has probably developed, as in our study.

If three examinations will be performed (the first two as above and also at 42–48 months of corrected age)

At 3½–4 years, testing of visual acuity becomes possible. A larger battery of tests is needed to evaluate further the wider visual function. Therefore, at least single and linear optotype testing should be done to reveal the pathological crowding phenomenon often seen in preterm children with neonatal ischaemic cerebral lesions.[13 27]

Follow up of children with cryotreated ROP and/or neurological sequelae

Regardless of available resources for ophthalmological follow up of prematurely born children, repeated ophthalmological follow up is needed for all children with severe ROP and/or with neurological complications, since they run the highest risk of ophthalmological complications. It is obvious, however, that no general guidelines can be given for this group of children.

Finally, in a society with well organised child healthcare centres and adequately trained staff, it is probably sufficient to have one ophthalmological follow up at around 1 year, provided that examination is totally normal and there is no history of severe ROP or neurological complications. If visual problems or strabismus are detected later at the healthcare centres, the child will be referred back to the ophthalmologist.

Bearing in mind the obvious risk of cerebral lesions, such as periventricular leucomalacia,[45] in preterm children and their effects on visual function,[13 27] a long term ophthalmological follow up with three examinations is advisable if no regular child health care is available.

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