ORIGINAL ARTICLES—Clinical science

Prospective study of New Zealand infants with birth weight less than 1500 g and screened for retinopathy of prematurity: visual outcome at age 7–8 years

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Abstract

***Aim*—To determine the visual outcome at 7–8 years in very low birth weight (VLBW: birth weight <1500 g) infants screened for retinopathy of prematurity (ROP).**

***Methods*—In 1986 all 413 VLBW infants admitted to neonatal units in New Zealand were enrolled in a prospective study of acute ROP. Surviving infants were traced and assessed at a home visit. Visual assessment comprised examination for abnormal and range of eye movements, visual fields, distance and near visual acuity, stereopsis, and photorefraction.**

***Results*—Of 338 infants surviving to discharge, 313 (93%) had been examined for acute ROP. ROP was present in 66 (21%: ROP+), absent in 247 (ROP−), with 25 not examined (NA). 298 children (96% survivors resident in New Zealand: 91% all survivors) were assessed. Any visual problem occurred in 79% ROP+ and 60% ROP−/NA ($p<0.01$). Distance visual acuity less than 4/10 in the worse eye occurred in 29% ROP+ and 15% ROP−/NA ($p<0.05$); and in the better eye in 19% ROP+ and 5% ROP−/NA ($p<0.001$). Any myopia in the worse eye occurred in 36% ROP+ and 18% ROP−/NA ($p<0.01$); and in the better eye in 25% ROP+ and 11% ROP−/NA ($p<0.01$). Strabismus, including treated, occurred in 33% ROP+ and 19% ROP−/NA ($p<0.05$). Overall, 11% had astigmatism and 18% hypermetropia with no difference between the groups.**

***Conclusion*—In a population based study it was confirmed that VLBW is associated with an increased risk of visual problems at school age. A history of ROP is associated with an additional risk of poor outcome, including a near doubling of poor distance acuity, myopia, and strabismus.**

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Of preschool children, between 5% and 10% are reported to have visual impairment while 2–5% have amblyopia.[1] By age 7, up to 13% of children will have some defect in visual acuity.[2] Both prematurity and low birth weight have been associated with an increased incidence of ophthalmic disorders, although the relative contributions to morbidity of regressed retinopathy of prematurity (ROP) and of prematurity itself are less certain.[3–7]

There have been few prospective population based studies of visual outcome in children who have been screened for acute ROP. In 1986 all infants born in New Zealand with birth weight less than 1500 g (very low birth weight; VLBW) and admitted to neonatal units were entered into a prospective audit of acute ROP.[8 9] Surviving children have now had their visual and neurological outcome assessed at 7–8 years of age. Overall neurodevelopmental outcome has been reported separately.[10]

Methods

In 1986 there were 52 824 live births in New Zealand; 413 VLBW infants were admitted to neonatal units with 338 (81.8%) surviving to discharge home. Before the 1986 audit, efforts were made to ensure that standards for screening for ROP were uniform. A paper was circulated on examination technique recommending the use of a speculum and scleral indentation.[11] The protocol called for all VLBW infants to be examined by an ophthalmologist skilled in indirect ophthalmoscopy, initially at 6 to 9 weeks of age, and to have further review if ROP was detected or the eye not fully vascularised. Cryotherapy was not available in New Zealand until the following year.

As part of the current study a check was made with the Department of Statistics for any infants born in 1986 with birth weight less than 1500 g who had subsequently died. The methods adopted to trace surviving children at age 7 years have been reported.[10] Once the family had given consent to participate in the study a time was made to visit the children in their homes, where all assessments were undertaken.

The assessment consisted of three parts. Firstly, the parents were given a questionnaire

Table 1 Details of children registered blind

Gestation (weeks)	*Birth weight (g)*	*Sex*	*Vision*	*Cause*	*Other abnormalities*
26	810	M	Light perception	ROP	Sacral agenesis: lower motor neuron palsy Not testable on WISC
25	670	F	Nil	ROP	None
26	840	F	Light perception	ROP	None
27	900	F	Light perception	ROP	Moderate CP. Not testable on WISC
25	670	M	Nil	ROP	Mild CP: epilepsy, >3 SD below mean on WISC
29	1061	F	Light perception	Cortical (no ROP)	Severe CP, PVL. Not testable on WISC
26	1001	M	Hand movement	Cortical (ROP stage 3, resolved)	Moderate CP. Not testable on WISC
29	1480	M	0.5/40 R and L	Optic nerve hypoplasia (no ROP)	Moderate CP. >3SD below mean on WISC

CP = cerebral palsy; WISC = Weschler Intelligence Scale for Children–Revised; PVL = periventricular leucomalacia.

comprising details of their child's health, utilisation of health services including visits to ophthalmologists, orthoptists and opticians, schooling, behaviour, family stress and problems, and family background. Secondly, a visual assessment was carried out (see below). Lastly, the child was tested with the Revised Weschler Intelligence Scale for Children (WISC-R).

VISUAL ASSESSMENT

A history of visits to ophthalmic specialists was obtained together with prescription of spectacles or contact lenses or visual aids. A family history of visual problems was obtained. Children were examined for the presence of nystagmus, strabismus using the cover test, full eye movements, and visual fields by confrontation. Distance vision was tested as follows. If the child knew his or her alphabet letters well, visual acuity was tested in standardised lighting using an internally illuminated box[12] and 4 metre logMAR charts.[13] Visual acuity has been reported using the Snellen notation and 4 metre scale. Eyes were tested individually with the child wearing spectacles if normally used. With the child 4 metres from the chart, he or she was asked to name an indicated letter on the 4/40 line. If a correct response was obtained, one or two letters were indicated on each line, except that once the 4/6 line was reached a response was required to all letters on that and lower lines. If the child could not see the top two letters at 4 metres, the testing distance was repeatedly reduced as necessary. For children unsure of their alphabet, 4 metre letter matching was used or, if too difficult, picture card matching. For children with vision worse than 0.5/40, vision was graded as light projection, hand movements, light perception, or no perception of light.

Near vision was tested naming individual letters for children who knew their alphabet well, otherwise with matching letters, with the card held in a reading position at a distance of one third of a metre and in good illumination. One eye was tested at a time.

Stereopsis was tested using the American Optical Random Dot Stereogram (Stereo Optical Co, Chicago, IL, USA) with the plates presented at a distance of 40 cm in good illumination.

Lastly, two portrait photographs were taken with an eccentric photorefraction camera (OptoCam, University of Auckland), using a standard procedure.[14] This method will reliably detect myopia greater than 2.00 dioptres (D) but only 75% of eyes with 1.00 to 1.75 D and 25% of eyes with 0.5 to 0.75 D. Hypermetropia of 1.0 D or more will be detected, as will 80% of eyes with 1.0 to 2.0 D of astigmatism and 100% with > 2.0 D.[15]

Six home visitors took part in the study, all with previous experience in administering the WISC-R. They attended a course in Christchurch to undergo training in the visual assessment procedures.

Statistical comparisons of visual outcomes between children who had acute ROP and remaining children in the cohort were based on χ^2 tests of independence.

The study was approved by the 14 area health board ethics committees existing in New Zealand in 1986.

Results

Of 413 VLBW infants admitted to New Zealand neonatal units in 1986, 338 (81.8%) survived to discharge home and of these 313 (93%) had been examined for acute ROP. Twelve children died after discharge from hospital and before 7 years of age; 17 children (5.2% survivors) were traced to overseas; the families of seven children (2.1% of survivors) declined to participate in the study; and four children (1.2%) of survivors remained untraced. Hence, 298 children (96.4% of surviving children resident in New Zealand; 91.4% of all survivors) had some assessment but two of these children did not have visual assessment having moved overseas before this was carried out. The mean age at assessment was 7.6 (SD 0.44) years.

ROP was present in 66/313 infants (21%) and absent in 247. Of 66 children with acute ROP (ROP+), 64 survived to age 7–8 years and 58 (91%) were assessed. Among these 58 children, the highest stage of acute ROP was stage 1 in 26, stage 2 in 20, stage 3 in seven, and stage 4 in five. Of 247 children examined for but without acute ROP (ROP−), 238 survived to age 7–8 years and 216 (91%) were assessed; and of 25 children not examined for acute ROP (NA), 24 survived to age 7–8 years and 22 (92%) were assessed.

Five children were blind from ROP and comprehensive information on their vision was available from the New Zealand School for the Blind. Six children (one with cortical blind-

Table 2 Comparison of visual abnormalities at 7–8 years in children with and without acute retinopathy of prematurity (ROP)

	ROP+	*ROP− (or NA)*	*Significance (χ^2)*	*Overall*
Number	58	238		296
Any visual abnormality	79%	60%	p<0.01	64%
Distance VA				
<4/10: worse eye	29%	15%	p<0.05	18%
<4/40: worse eye	12%	1%	p<0.001	3%
<4/10: better eye	19%	5%	p<0.001	8%
<4/40: better eye	10%	1%	p<0.001	3%
Near VA worse than N.5				
worse eye	16%	8%	NS	10%
better eye	14%	5%	p<0.05	6%
Photoscreen myopia*, any:				
worse eye	36%	18%	p<0.01	21%
better eye	25%	11%	p<0.01	14%
Photoscreen hypermetropia*, any	17%	19%	NS	18%
Photoscreen astigmatism*, any	6%	12%	NS	11%
Strabismus (includes treated)	33%	19%	p<0.05	22%
Stereopsis* worse than 140°	14%	14%	NS	14%
Spectacles prescribed	40%	16%	p<0.001	21%

*Children blind from ROP have been excluded from photoscreen and stereopsis data. ROP+ = acute retinopathy of prematurity present; ROP− = acute retinopathy of prematurity not present; NA = not examined for acute retinopathy of prematurity; VA = visual acuity.

ness, one with severe cerebral palsy, one with autism, and three with attention deficit disorder) could not be tested on distance vision. Six children (one with autism, five because of camera failure) were not tested by photorefraction. In only two children was there no information either from distance vision testing, photorefraction, or other sources.

Eight children were registered blind (vision less than 4/40: Table 1). All five children with grade 5 ROP had a birth weight less than 1000 g and gestation less than 28 weeks (mean 778 g; 25.8 weeks). The incidence of blindness overall was 19.3 per 1000 live births with birth weight less than 1500 g. Of the seven children whose parents declined to participate in the study, one (also with birth weight less than 1000 g and gestation less than 28 weeks) was known to have bilateral blindness from ROP, and if included would increase the incidence of blindness to 21.7 per 1000 live births.

Overall, 64% of children had some visual abnormality with significantly more children who had had acute ROP having a visual problem than children who did not have acute ROP (Table 2). (In all cases children who were not examined for ROP had rates of abnormalities that were similar to, or lower than, those of the ROP− children and so have been included with this group). There were no differences in rates of hypermetropia between the groups and if this is excluded, the overall rate of visual abnormality reduces to 56%.

By photoscreen assessment, mild (0.5–2.00 D) and moderate/severe (> 2 D) myopia in the better eye occurred in 8% and 17% of ROP+, and 10% and 1% of ROP−/NA children ($p < 0.001$). In the worse eye, figures were 19% and 17% of ROP+, and 15% and 3% of ROP−/NA ($p < 0.001$) respectively.

We were unable to clearly identify which children had amblyopia because we did not examine the fundi to exclude retinal disease as a cause of diminished visual acuity. However, amblyopia may be present where there is strabismus (which was significantly more frequent in ROP+ children; Table 2); where distance visual acuity varied by more than two levels between eyes (ROP+ 10.3% versus ROP−/NA 7.6%: NS); or where this latter category is combined with strabismus (ROP+ 3.5% versus ROP−/NA 4.6%: NS).

Table 3 Highest stage of acute ROP and later visual acuity: individual eyes

		Visual acuity		
Stage ROP	*No of eyes*	*4/8 or better No (%)*	*4/10–4/40 No (%)*	*<4/40 No (%)*
None	480	430 (90)	45 (9)	5 (1)
Stage 1	49	45 (92)	3 (6)	2 (2)
Stage 2	39	30 (77)	9 (23)	—
Stage 3	10	7 (70)	1 (10)	2 (20)
Stage 4	10	—	—	10 (100)

The highest stage of acute ROP was significantly associated with subsequent visual outcome. Any visual abnormality was seen in 60% children in both ROP− and NA groups, 62% of those with stage 1 ROP, but 90% with stage 2 and 100% of those with stage 3 or 4. The visual acuity for individual eyes related to the highest stage of acute ROP is shown in Table 3.

Discussion

In this prospective population based study of VLBW infants we have detected a high incidence of ophthalmic abnormalities at 7–8 years of age; nearly two thirds of the cohort having some abnormality and one in five children having spectacles prescribed. The presence of acute ROP of any stage in the neonatal period was associated with a near doubling of poor distance and near visual acuity, photoscreen myopia, and strabismus compared with rates observed in infants with no acute ROP. Rates of significant hypermetropia, astigmatism, and poor stereopsis were no different between the groups.

We chose to visit children in their homes in order to achieve the highest possible follow up. We also used non-medically qualified home visitors who were skilled in using the WISC-R. Although these visitors were trained in the techniques of visual assessment, this meant that fundal examination was not carried out and hence we were unable to distinguish between cicatricial and regressed ROP. Additionally, photorefraction was used which should detect all refractive errors of more than 2.00 D but may miss some more minor degrees of refractive error. If anything this will mean we may have underestimated the rate of visual abnormalities, although we are unlikely to have failed to detect significant functional problems.

The present study also did not include a contemporary control group of infants born at term because to do so would have greatly increased the cost and presented numerous logistical problems. Comprehensive information on vision and eye problems at age 7 in New Zealand children is available from a study of 988 Dunedin children born in 1972/73, which cohort included no VLBW children.[16] In this group any visual abnormality occurred in 9.4%. Distance visual acuity of less than 6/12 occurred in the better eye in 2.2% and worse eye in 5.5% of children. Near visual acuity worse than N5 occurred in the better eye in

Table 4 Myopia following acute ROP: studies with follow up beyond 1 year

Author	*Criteria*	*Study method*	*Age at follow up*	*No of children*	*Myopia*	*% with myopia*	
Cats, Tan[3] 1989	<32 weeks 32–34 in O_2	Unit based prospective	6–10 years	42+ 42−	>1D	29% 10%	19%
Quinn *et al*[f] 1992	<1251 g	Multicentre prospective	2 years	597+[a] 356−[a]	>0.25D	24% 13%	20%
Page *et al*[36] 1993	<1251 g	Unit based retrospective	12 months	58+[a] 52−[a]	>0.25D	21% 11%	16%
			24 months	27+[a] 23−[a]	>0.25D		38%
Robinson, O'Keefe[37] 1993	<1500 g +/− <30 weeks	Unit based prospective	Up to 5 years	160+[a] 102−[a]	>1D	28% 9%	20%
This study	<1500 g	Geographical prospective	7–8 years	52+ 234−	>0.25D[b]	25–36%[c] 11–18%[c]	19–33%[c]

D = dioptres; + = ROP present; − = ROP not present; a = number of eyes; b = see text; c = respectively better and worse eye.

1.0% and worse eye in 4.4%. Strabismus occurred in 3.9% and 3.6% of children had had spectacles prescribed. There is nothing to suggest any change in the overall incidence of childhood visual disorders in New Zealand in recent years. Comparing our data with these Dunedin data it is clear that VLBW, even in the absence of ROP, does greatly increase the risk of visual disorders by 7 years, and for important outcomes by two to three times.

There have been few population based studies which have comprehensively assessed visual outcome in VLBW infants related to the presence or absence of acute ROP,[17–20] and the differing study design and method of reporting makes comparison with this study difficult. The study from the East Midland Region of the UK is perhaps closest to ours in design[21] but has not reported on visual outcomes beyond the first year of life.[19] The important population based cohorts from Canada[22] and Australia[23] included only infants with birth weight less than 1000 g and focused primarily on overall neurodevelopmental status. Much information is becoming available from the natural history arm of the large multicentre CRYOROP study[7 24 25] but this study only included infants with birth weight less than 1251 g and needs to be interpreted alongside population based data.

Although our rate of visual abnormalities is high, other studies have also found high rates of visual problems in ex-very premature children. A report from the Oxford Region found 59% of surviving infants with birth weight less than 1000 g had ocular abnormalities at 3–5 years of age.[18] A study from Sweden reported 25% of children born < 33 weeks' gestation or with birth weight <1501 g in Stockholm County had been referred for ophthalmic care aged 5–10 years, compared with 11.5% of term children.[26 27] A number of unit based studies report similar data. Dowdeswell and others found some ocular pathology at age 5–7½ years in 45% of surviving infants with gestation less than 32 weeks, compared with 13% term controls from the south west of England.[28] Two studies from the Netherlands have reported visual impairments in 54% of VLBW infants at 1 year of age and 45% of premature infants at 6–10 years of age.[3 29] With the exception of the study by Cats and Tan,[3] appropriate screening for acute ROP was not carried out in these studies, hence no inferences can be made about the contribution of ROP to visual outcome.

It is well recognised that refractive errors, amblyopia, and astigmatism are common in premature and very low birthweight infants whether or not they have suffered acute ROP.[5 6 30] Approximately 90% of cases of acute ROP will spontaneously regress[31] but it has been unclear whether completely resolved ROP is associated with any visual sequelae, or alternatively whether visual problems in premature infants may be the result of unrecognised ROP.

Many studies have reported increased rates of myopia in children who have suffered acute ROP.[3 5 7 30 32–37] Recent studies with follow up beyond 1 year of age and in which infants had been screened for acute ROP are shown in Table 4. These studies all show approximately twice the rate of myopia following acute ROP compared with absence of ROP; the overall rates in both groups being similar to the present study.

It has been suggested that myopia of prematurity tends to regress during the first year of life resulting in emmetropic or hyperopic refractions later, but when ROP develops this shift does not occur.[3] If this is what takes place there may be an expectation that rates of hypermetropia would be lower in infants with ROP compared with those without. However, both in the present study and that of Cats and Tan (who reported 11% hypermetropia ⩾ 1 D overall)[3] there was no such difference between the groups. It may be that milder degrees of ROP, in terms of both stage and location, have less effect on ocular growth, as has been suggested by both the CRYOROP study[7] and the East Midlands study.[19] The relation between prematurity, acute ROP, ocular growth and development, and subsequent refractive index has been discussed[4 7 19] and possible contributing mechanisms include influences on corneal curvature,[38] lens thickness,[39] anterior chamber depth,[40] as well as axial length.

While it is clear that more severe ROP is associated with overall worse outcome it remains controversial as to whether regressed stage 1 and 2 disease is associated with visual sequelae. Data from the CRYOROP study confirm that serious adverse outcome (defined as a retinal fold involving the macular, retrolental opacity encroaching on the pupil or partial or complete retinal detachment) is rare

after stage 1 or 2 disease other than in zone 1.[25] On the other hand in that study, stage 2, zone 2 disease was associated with nearly twice the rate of subsequent myopia compared with no ROP, as well as an increased risk of strabismus.[7 25] Our data would support this view (Table 3), with stage 2 disease, but not stage 1, increasing the risk of mildly reduced visual acuity. The implication of this is that any child who has had acute ROP should be followed at 1 and 2 years of age to check acuity and refraction as a minimum.

We found an overall rate of strabismus of 22%, similar to that observed in other studies,[3 18 35 37 41] although Page and others[36] reported lesser rates at 12 and 24 months of age. Most studies do suggest strabismus is nearly twice as frequent after acute ROP compared with similar infants without ROP.[3 25 35] Only Robinson and O'Keefe found a higher rate in infants without ROP and there is no clear cut explanation for this.[37]

There has been some debate as to whether the use of antenatal steroids, given to reduce the risk of hyaline membrane disease, may be associated with a reduction in the incidence of blindness from ROP such that cortical blindness is now the more common cause of blindness in premature infants.[42] Since the pioneering work of Liggins and Howie[43] New Zealand has had high rates of antenatal steroid usage and 60% of this cohort received a full or partial course in utero. Cryotherapy was not available in New Zealand in 1986 but had it been, the number of eyes with adverse visual outcome may have been reduced by nearly 50%, which may have meant children with blindness from ROP were either the same number or fewer than those with blindness from other causes (principally cortical blindness). Given that there are likely to be some children with cortical blindness, but not blindness from ROP, who had birth weight greater than 1500 g, it does seem plausible that blindness due to the former may exceed that due to ROP. However, this study suggests that if there is a decline in blindness from ROP it is more likely to be due to appropriate screening and treatment with cryotherapy than to antenatal steroid usage.

In conclusion, despite a number of unavoidable limitations in our study design, our data provide further evidence that VLBW greatly increases the risk of childhood visual disorders, and that a history of ROP is associated with some additional risk, including a near doubling of reduced visual acuity, myopia, and strabismus.

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