Vision in former very low birthweight young adults with and without retinopathy of prematurity compared with term born controls: the NZ 1986 VLBW follow-up study

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ABSTRACT

Objective There are few data on visual outcomes in adulthood of former very low birthweight (VLBW; <1500 g) infants. We aimed to assess vision at 27–29 years in a national cohort of VLBW infants born in 1986 and assessed for retinopathy of prematurity (ROP) when no treatment was available, compared with term born controls.

Methods The cohort and controls attended a 2-day assessment in Christchurch as part of a larger study. Visual assessment included glasses prescription measured by focimeter, logarithm of the minimum angle of resolution (logMAR) distance visual acuity (VA), contrast sensitivity, autorefraction, retinal photographs and a questionnaire on vision-related everyday activities. Rates of reduced VA and myopia in the VLBW cohort at 27–29 were compared with the results of vision testing at 7–8 years.

Results 250 VLBW adults (77% those alive) gave study consent and 229 (45 with a history of ROP) were assessed in Christchurch, plus 100 term born controls. VLBW adults with ROP had reduced VA compared with no ROP and controls (mean logMAR score (SD); 0.003 (0.19), –0.021 (0.16), –0.078 (0.09), P=0.001). There were no differences in myopia (>2 D) between the groups but high myopia (>5 D) was confined to those with ROP. VLBW adults with ROP drove a car less often and had higher difficulties with everyday activities scores due to eyesight. Between 7–8 and 27–29 years rates of reduced VA were stable but myopia increased.

Conclusion Former VLBW young adults with ROP have ongoing problems with vision affecting daily living and should continue in regular ophthalmological review.

Trial registration number ACTRN12612000995875, Pre-results .

INTRODUCTION

There are few comprehensive data on visual outcomes in adult former very preterm (VP; <32 weeks' gestation) or very low birthweight (VLBW; <1500 g birth weight) infants although it is known that in early and middle childhood there is an increased risk of problems such as myopia, strabismus and amblyopia as well as cerebral visual impairment associated with white matter damage.[1 2] Visual outcomes in VLBW infants will be impacted by the presence of retinopathy of prematurity (ROP) and its severity and treatment and by other morbidities.[1–4] In a Swedish population-based prospective study of 213 VLBW children and 217 term controls, aged 10 years, significant refractive errors (1 D or more) occurred in 8% controls, 26% VLBW with no ROP and 64% those with severe treated ROP.[5]

There are many VP/VLBW young adults born in the 1970s and early 1980s in high-income countries who had ROP but were not treated and it is important to be aware of the visual outcomes for these individuals. Furthermore, in many low-income and middle-income countries both adequate examination for ROP and appropriate treatment is unfortunately often unavailable for high-risk infants, adding to the pool of individuals with untreated ROP.[6]

In the present study we aimed first to assess visual outcomes at 27–29 years of age in a national cohort of VLBW infants born in 1986 and before ROP treatment was available, compared with healthy term born controls, and second to assess whether rates of poor visual acuity (VA) and myopia were stable between 7–8 years and young adulthood in the VLBW cohort.

METHODS

The prospective New Zealand VLBW Follow-up Study cohort included all 413 VLBW infants born in 1986 and admitted to a neonatal unit, of whom 338 (82%) survived to discharge home.[7] Of these infants, 313 were examined for ROP; any ROP occurring in 67 (21%) and stage 3 or more in 12 (3.8%), including six children, all with birth weight <1000 g, who were bilaterally blind.[8] The cohort were followed up at 7–8 years, when comprehensive visual assessment was undertaken in the child's home.[9] In the present study, 250 members of the VLBW cohort (77% of 323 known survivors) gave consent for follow-up, with 229 being assessed over 2 days in Christchurch together with 100 controls born full term in New Zealand in 1986, aged 27–29 years.[7]

The visual assessment component, taking approximately 1 hour, comprised verifying any glasses prescription by means of a focimeter (Topcon CL-100, Topcon, Tokyo, Japan); distance VA assessed using the standardised, retro-illuminated 4 m ETDRS logarithm of the minimum angle of resolution (LogMAR) chart (at the recommended photopic test level of 85 cd/m^2 and remaining in the same location for the duration of the study) with

glasses if worn; contrast sensitivity using the Pelli-Robson chart; autorefraction (Nidek Tonoref II, Nidek, Gamagori, Japan); retinal photographs following instillation of tropicamide 1% eye drops; and the National Eye Institute Visual Functioning Q-25 (NEI-25) questionnaire on visual functioning and everyday activities.[10] From the autorefraction we calculated spherical equivalents. We defined moderate visual impairment as any of VA >0.3 (Snellen <20/40), myopia >2.0 D, hypermetropia >2.0 D or astigmatism of >2.0 D in the better eye. Assessors were not blinded to participants' grouping, other than for retinal photographs.

Between group differences were tested for statistical significance using the χ^2 test of independence for comparison of percentages and one-way analysis of variance for comparison of means.

All participants gave written informed consent.

RESULTS

Questionnaire information was available from 250 VLBW young adults and 100 controls. There were few overall perinatal and demographic differences between surviving VLBW young adults assessed at 27–29 years and not assessed apart from slightly more males in the latter group (online supplementary table 1). Nine (12.3%) of those not assessed had ROP, including 4 with stage 3 or more, compared with 54 (21.6%) who were assessed.

Of the 229 VLBW cohort assessed in Christchurch, 45 had a history of ROP. Four were known to be blind, three as a result of ROP and one with optic nerve hypoplasia. Among 21 VLBW adults providing only questionnaire information, 9 had a history of ROP, including 1 individual with blindness from ROP. There were 222 VLBW (43 with ROP) who underwent visual assessment at both 7–8 years and 27–29 years.

There were clear and significant differences in VA between the VLBW cohort and controls (table 1A–C). VA was significantly decreased in VLBW adults with a history of ROP compared with VLBW adults without ROP and in those with birth weight <1000 g compared with 1000 g or more. We did not observe any difference in the incidence of myopia (>2 D) between the groups. However, severe myopia (>5.0 D) was significantly more common in VLBW adults with a history of ROP or those with birth weight <1000 g and otherwise occurred only infrequently. There was no difference in the incidence of hypermetropia (>2.0 D) between the groups but astigmatism (>2.0 D) occurred more frequently in VLBW adults compared with controls. Glasses were worn by a similar proportion of all groups. There were also no differences detected by contrast sensitivity testing between the groups and this result was not altered by examining different cut-points on the distribution of contrast sensitivity or by when VLBW adults were classified by ROP or birthweight status. Retinal photograph abnormalities were infrequent and not significantly different between the groups. In the VLBW group abnormalities included macular changes (4), retinal artery tortuosity (4) and retinal telangiectasis (3). Moderate visual impairment was not different between VLBW young adults and controls but was seen significantly more frequently in VLBW young adults with a history of ROP (33.3% compared with 20.1% in VLBW without ROP and 14.0% controls).

These results were similar when we considered VA and myopia data by better or worse eye (online supplementary table 2A,B). Considering all eyes, birth weight <1000 g compared with ≥1000 g was associated with poorer VA (online supplementary table 2C) but did not impact on the level of myopia (online supplementary table 2D). The stage of ROP had an impact on

Table 1 Vision screening outcomes in VLBW survivors at age 27–29 years compared with term born controls

Measure	VLBW (n=229)	Controls (n=100)	P value
(A) VLBW vs controls			
Visual acuity (better eye)			
Mean (SD) logMAR score*	−0.017 (0.163)	−0.078 (0.086)	0.001
% logMAR>0	32.8	13.0	0.001
% logMAR>0.3	7.4	0.0	0.005
Autorefraction (better eye)*			
% myopia (≥0.5 D)	50.2	44.0	NS
% myopia (>2.0 D)	13.3	12.0	NS
% myopia (>5.0 D)	3.6	1.0	NS
% hypermetropia (>2.0 D)	1.8	2.0	NS
% astigmatism (>2.0 D)	6.2	1.0	0.04
Contrast sensitivity (better eye)			
Mean (SD) sensitivity*	1.75 (0.14)	1.76 (0.13)	NS
% Abnormal eye photo*†	7.5	3.2	NS
% Visual impairment (moderate)‡	22.7	14	NS
% Wear glasses	24.9	30	NS

Measure	VLBW ROP (n=45)	VLBW No ROP (n=184)	Controls (n=100)	P value
(B) VLBW by history of ROP vs controls				
Visual acuity (better eye)				
Mean (SD) logMAR score*	0.003 (0.190)	−0.021 (0.157)	−0.078 (0.086)	0.001
% logMAR>0	33.3	32.6	13.0	0.001
% logMAR>0.3	17.8	4.9	0	0.001
pAutorefraction (better eye)*				
% myopia (≥0.5 D)	40.5	52.5	44	NS
% myopia (>2.0 D)	21.4	11.5	12	NS
% myopia (>5.0 D)	11.9	1.6	1	0.001
% hypermetropia (>2.0 D)	0	2.2	2	NS
% astigmatism (>2.0 D)	4.8	6.6	1	NS
Contrast sensitivity (better eye)				
Mean (SD) sensitivity*	1.74 (0.16)	1.75 (0.13)	1.76 (0.13)	NS
% Abnormal eye photo*†	11.1	6.8	3.2	NS
% Visual impairment (moderate)‡	33.3	20.1	14	0.03
% Wear glasses	20.0	26.1	30	NS

Measure	VLBW <1000 g (n=64)	VLBW ≥1000 g (n=165)	Controls (n=100)	P value
(C) VLBW by birth weight <1000 g vs controls				
Visual acuity (better eye)				
Mean (SD) logMAR score*	0.018 (0.182)	−0.029 (0.155)	−0.078 (0.086)	0.001
% logMAR>0	42.2	29.1	13	0.001
% logMAR>0.3	15.6	4.2	0	0.001
Autorefraction (better eye)*				
% myopia (≥0.5 D)	47.5	51.2	44	NS
% myopia (>2.0 D)	18.0	11.6	12	NS
% myopia (>5.0 D)	8.2	1.8	1	0.02
% hypermetropia (>2.0 D)	1.6	1.8	2	NS

Continued

Table 1 Continued

Measure	VLBW <1000 g (n=64)	VLBW ≥1000 g (n=165)	Controls (n=100)	P value
% astigmatism (>2.0 D)	4.9	6.7	1	NS
Contrast sensitivity (better eye)				
Mean (SD) sensitivity*	1.75 (0.15)	1.75 (0.13)	1.76 (0.13)	NS
% Abnormal eye photo*†	13.3	5.6	3.2	0.06
% Visual impairment (moderate)‡	32.8	18.8	14	0.01
% Wear glasses	26.6	24.2	30	NS

*Excludes three ROP adults, two with some light perception and one with none.
†Excludes 38 VLBW and 5 controls unable to obtain acceptable eye photo due to problems with pupil dilation, eye movement or other factors.
‡Any of visual acuity >0.3 LogMAR, myopia >2 D, hypermetropia >2 D or astigmatism >2 D in the better eye.
LogMAR, logarithm of the minimum angle of resolution; ROP, retinopathy for prematurity; VLBW, very low birthweight.

VA in that the proportion of eyes with logMAR >0.30 was two to three times higher after stage 2 or more ROP compared with stage 1 or no ROP (online supplementary table 2E). Similarly high myopia (>5 D) was seen in 24% of eyes with stage 2 ROP but 2.5% and 1.9% of eyes with stage 1 or no ROP (supplementary table 2F).

Table 2 gives details of VLBW young adults with severe loss of vision. At discharge from hospital in the neonatal period there were six infants, all with birth weights <1000 g, who were bilaterally blind from ROP. Three of these young adults were assessed at 27–29 years when two had some light perception and both were living largely independent lives. The parent of a further young adult, who was blind from ROP and had other severe impairments, answered a questionnaire. At 7–8 years three other children were registered as blind. Two had a diagnosis of cerebral visual impairment and the parent of one provided questionnaire information at 27 years. The third child was known to have optic nerve hypoplasia and at 27 years VA showed moderate visual impairment (logMAR 0.6 and 0.9) but also with very little peripheral vision. Five VLBW young adults had severe unilateral vision loss including two who had suffered a retinal detachment, both at age 16 years. Both had been recorded as having stage 2 ROP, one with plus disease. At 7–8 years the former had myopia >2 D and the latter 1 D. Surgery resulted in light perception and finger counting only for the affected eyes respectively.

Reported eye problems on the NEI-25 questionnaire (table 3A–C) were more frequent in those with ROP or birth weight <1000 g compared with other groups. And VLBW young adults had higher 'difficulties with everyday activities' scores due to eyesight, which included reading signs, cooking, attending shows and observing people's reactions and which was significant for those with ROP. Fewer VLBW (80%) than controls (96%) drove a car, although this difference was sometimes attributable to factors other than eyesight. And those with a history of ROP, who did have a driving licence, reported difficulties with driving due to eyesight problems significantly more frequently.

Of 222 VLBW young adults, 43 with ROP, who were also assessed at 7–8 years, analysable data were available from 218. Overall rates of poor VA (logMAR >0.3) were similar at both time points being for those with and without ROP 14.3% and 4.6% at 7–8 years, and 16.3% and 5.0% as young adults. By contrast the rates of any myopia (≥0.5 D) increased over time, being for those with and without ROP 22.0% and 11.3% at 7–8 years, and 41.5% and 52.8% as young adults.

DISCUSSION

In this prospectively enrolled national cohort of VLBW young adults we have confirmed that both preterm birth and ROP have an impact on long-term visual morbidity. To obtain a driver's licence in New Zealand, VA must be logMAR 0.3 or better in at least one eye and VA >0.3 in the better eye occurred in 17.8%

Table 2 Severe loss of vision in VLBW cohort at 7–8 years and 27–29 years

Gestation (weeks)	Birth weight (g)	Sex	ROP	Seen 7–8 years	Seen 27–29 years	Vision status 27–29 years	Other problems
Severe bilateral vision loss							
26	810	M	S 4	Yes	Questionnaire only	Nil	Sacral agenesis, epilepsy
27	900	F	S 4	Yes	No	(Light perception at 7 years)	Moderate CP
25	670	M	S 4	Yes	No	(Nil at 7 years)	Mild CP, epilepsy
25	923	M	S 4	No	Yes	Light perception on R None on L	
25	670	F	S 4	Yes	Yes	Nil	
26	840	F	S 4	Yes	Yes	Light perception R and L	
29	1061	F	None	Yes	No	(Cerebral visual impairment)	Severe CP
29	1480	M	None	Yes	Yes	Optic nerve hypoplasia, registered blind at 7–8 years VA 0.6 on R; 0.9 on L	Moderate CP, epilepsy. Intellectual impairment
26	750	M	S 3 plus, resolved	Yes	Questionnaire only	Cerebral visual impairment	Severe CP, epilepsy. Not testable
Other severe unilateral vision loss							
27	1460	M	None	Yes	Yes	Bilateral cataracts, removed L VA 0.94 on R; 0.14 on L	
26	880	M	S 2	Yes	Yes	L retinal detachment 16 years VA −0.04 on R; finger count L	
26	930	M	S 2 plus	Yes	Yes	R retinal detachment 16 years Light perception R; VA −0.1 L	
29	780	F	S 2	Yes	Yes	L eye corneal scarring VA 0.32 on R; 0.86 on L	
28	1027	M	None	Yes	Yes	L eye penetrating injury 8 years VA −0.06 on R; count fingers L	

CP, cerebral palsy; L, left; R, right; ROP, retinopathy of prematurity; VA, visual acuity; VLBW, very low birthweight.

Table 3 Results of visual functioning questionnaire in VLBW survivors at age 27–29 years compared with term born controls

Measure	VLBW (n=250)	Controls (n=100)	P value
(A) VLBW vs controls			
% Rating eyesight as good or excellent (with glasses, contacts)	86.8	91	NS
% Worried about eyesight	27.6	28	NS
Mean (SD) difficulties with everyday activities score (other than driving, due to eyesight)	13.1 (6.5)	11.7 (1.5)	0.03
% Who drive a car*	78.8	96	0.001
Mean driving difficulties score (due to eyesight)†	3.9 (1.6)	3.5 (1)	0.02

Measure	VLBW		Controls	P value
	ROP (n=54)	No ROP (n=196)	(n=100)	
(B) VLBW by history of ROP vs controls				
% Rating eyesight as good or excellent (with glasses, contacts)	77.8	89.3	91	0.04
% Worried about eyesight	35.2	25.5	28	NS
Mean (SD) difficulties with everyday activities score (other than driving, due to eyesight)	15.9 (11.2)	12.4 (4.1)	11.7 (1.4)	0.001
% Who drive a car*	74.1	80.1	96	0.001
Mean driving difficulties score (due to eyesight)†	4.7 (2.2)	3.7 (1.4)	3.5 (1)	0.001

Measure	VLBW		Controls	P value
	<1000 g (n=68)	≥1000 g (n=182)	(n=100)	
(C) VLBW by birth weight (<1000 g) vs controls				
% Rating eyesight as good or excellent (with glasses, contacts)	83.8	87.9	91	NS
% Worried about eyesight	33.8	25.3	28	NS
Mean (SD) difficulties with everyday activities score (other than driving, due to eyesight)	15.1 (10.2)	12.4 (4.2)	11.7 (1.5)	0.001
% Who drive a car*	76.5	79.7	96	0.001
Mean driving difficulties score (due to eyesight)†	4.3 (2.1)	3.7 (1.4)	3.5 (1.0)	0.002

*The difference in the percentage who drive a car is largely attributable to factors other than vision problems including cognitive impairment or physical disability.
†Limited to drivers only (VLBW n=196, controls n=96).
ROP, retinopathy of prematurity; VLBW, very low birthweight.

of VLBW young adults with ROP, 4.9% of those without ROP and none of controls (P<0.001). The impact of VLBW on any myopia was less except that high myopia (>5 D) was virtually confined to individuals with ROP and those with <1000 g birth weight. Astigmatism of >2 D in the better eye occurred more frequently in the VLBW group. There were no differences in the proportion of the VLBW cohort and controls who wore glasses, however a rating of eyesight as less than good and increased self-reported difficulties with everyday activities and driving were more frequent in those with a history of ROP.

For the overall group the rate of poor VA remained fairly stable between childhood and young adulthood. Over the same period rates of mild myopia increased regardless of whether there was a history of ROP. In a subsequent report we will assess on an individual basis how predictive visual findings at 7–8 years were for young adult vision.

The strengths of our study include that this is a national population-based cohort who underwent screening for ROP, with longitudinal data following a comprehensive visual assessment at 7–8 years of age and the relatively high (77%) follow-up rate to 27–29 years. Weaknesses include the rather limited assessments we undertook given time and funding constraints, hence we did not assess eye movements and binocular vision, visual fields or visual processing and the relatively small number of individuals with ROP. In 1986 we did not report on plus disease and there were 25 children who did not have retinal examinations for ROP, however they were mostly of higher gestation and birth weight (mean gestation 31.2 weeks, range 26–36; mean birth weight 1259 g, range 850–1480 g).

The data show that untreated ROP of stage 2 or more, which did not progress to bilateral detachment, did have a significant impact on both decreased VA and increasing severity of myopia (online supplementary table 2E,F), which is similar to our findings at 7–8 years.[9] By contrast several studies suggest that while VP/VLBW children have poorer VA than controls, mild (stages 1 or 2) ROP eyes have similar outcomes to no ROP.[3 11] In 1986 a number of infants had retinal examinations outside of the main centres, where there was less experience with ROP so it is possible some eyes were misclassified. Recent trends to capture permanent digital images at the time of retinal examination that can be interpreted either locally or remotely by trained experts may go some way to eliminate diagnostic variations between centres regardless of geography.[12]

With current ROP screening and treatment programmes severe visual impairment from ROP in very preterm infants is now uncommon in high-income countries at around 1%.[13 14] Given this it seems likely that had laser therapy been available and Early Treatment for Retinopathy of Prematurity study (ET-ROP) criteria followed in 1986 useful vision might have been preserved in most of the six individuals who progressed to bilateral retinal detachments. Excluding these infants there were 21 others who had plus disease (Darlow, unpublished data, 1986), thus meeting ET-ROP type 1 criteria for treatment,[15] and 12 of these underwent visual assessments at 27–29 years. Two-thirds of this group had no or only mild visual impairment and one-third moderate visual impairment in the better eye. None had 'unfavourable' VA (Snellen ≤20/200; logMAR ≥1) as defined by the ET-ROP study.[16] In the ET-ROP study, 52% of high-risk eyes not yet reaching type 1 criteria underwent regression without treatment[16] and overall between one and two out of every three treated eyes could well have had a good outcome without treatment.[17] Comparing our

results directly with ET-ROP is difficult because more infants in that study had zone I disease but our data do provide some support for the conclusion that eyes which have not reached type 1 criteria should not be treated, even though such treatment seems to occur quite frequently.[18 19]

There are relatively few long-term studies on the natural history of untreated ROP, especially from the era of more modern neonatal care. In patients aged 45 years or more who had been diagnosed with retrolental fibroplasia following birth in 1946–1964, 88% of eyes had posterior segment pathology, 91% were myopic and 84% had cataracts. VA was 20/200 (logMAR 1) or worse (legally blind) in 51% eyes.[20] Treatment for ROP was established as a result of the large Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) trial and a subset of 1068 infants, with birth weight <1251 g and born from 1986 to 1987, enrolled in the natural history arm of that trial were followed up at 5½ years.[21] Unfavourable VA (20/200 or worse) occurred in 5.1% eyes. In the same group of infants, Quinn *et al* reported that among children with ROP 20% had myopia (>0.5 D) and 6.5% high myopia (>5 D) compared with 7.1% and 1.8% of children without ROP.[22] We found that 11.9% young adults with a history of ROP had high myopia compared with 1.6% without ROP. There is some debate about the causes of myopia following ROP[4] and this does warrant further investigation. In addition, there is a lack of information about astigmatism in ex-preterm infants, with and without ROP, beyond childhood[3] and we plan to provide a fuller report on this aspect in a subsequent publication.

Ophthalmic follow-up of population-based studies of VLBW infants from the pre-treatment era, prospectively examined for ROP, has also been reported in middle childhood from Denmark[23 24] and England.[25 26] Severe visual impairment occurred in 3%–4% of these children.[2] Saigal *et al* reported that six young adults (4% of 142 born in Canada from 1977 to 1982 with birth weight <1000 g and followed up prospectively) had experienced a late retinal detachment by age 23 years.[27] There were two cases of retinal detachment occurring in our cohort at 16 years and we would recommend that adolescents and young adults who have had ROP are aware of this potential complication and remain under ophthalmology review.[4 28] The Canadian study also recently reported that ROP was independently related to dysglycemia in young adulthood suggesting possible common pathogenic mechanisms.[29] We have investigated cardiometabolic health in our cohort also, which will be reported separately.

Even though vision loss is now infrequent there remains considerable other visual morbidity and children with ROP requiring treatment are also at greater risk of motor and cognitive impairment.[30] In addition, a prospective, population-based study of extremely low birthweight (ELBW) children from Victoria, Australia, born in the era of ROP treatment, reported more problems in visual perception at age 14–20 years (OR 3.09) compared with controls.[31] A subsequent MRI study in the same ELBW cohort reported alterations in both the optical radiation and visual cortex compared with controls, which may be related to the visual findings.[32] We have undertaken cranial MRI scans on a subset of our participants and these results will be reported separately.

In conclusion, VLBW young adults born in New Zealand in 1986 had similar rates of moderate visual impairment as their term born peers. However, VLBW young adults did more often have difficulties with everyday activities due to eyesight and less frequently drove a car. In the VLBW cohort, a history of untreated ROP was associated with reduced VA, a higher likelihood of high myopia and an increased risk of suffering a late retinal detachment, and we recommend these young people should continue to have regular ophthalmological review.

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Contributors BAD conceptualised and designed the study, contributed to the interpretation of data, drafted the initial manuscript and approved the final manuscript as submitted. MJE, BK, JM and LJH contributed to the concept, design and interpretation of data, critically reviewed and revised the draft manuscript for intellectual content and approved the final submitted version of the article. All authors agree to be accountable for all aspects of the work presented, including the accuracy and integrity of the findings reported. BAD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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