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Ophthalmological outcome of 6.5 years children treated for retinopathy of prematurity: a Swedish register study

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ABSTRACT

Aims To determine the ophthalmological outcome at 6.5 years of age in children treated for retinopathy of prematurity (ROP), and registered in the national Swedish National Register for ROP register.

Methods Data on ROP, treatment and ophthalmological outcome were retrieved from the register. Visual acuity (VA), refractive errors and strabismus, together with visual impairment (VI) and any significant eye problem, defined as VA >0.5 logarithm of the minimal angle of resolution (logMAR) and/or strabismus and/or any refractive error were analysed. Risk factors such as sex, gestational age (GA), birth weight SD score, number of treatments and retreatments, postnatal age and postmenstrual age at first treatment were analysed.

Results Follow-up data were available in 232 of 270 children born between 2007 and 2014 who had been treated for ROP. VI (VA >0.5 logMAR) was found in 32 (14%), strabismus in 82 (38%), refractive errors in 114 (52%) and significant eye problem in 143 (65%) children. Retreatment was a risk factor for VI and refractive errors. Male sex and neonatal brain lesion were risk factors for strabismus. An additional week of GA at birth reduced the risk for refractive errors, strabismus and significant eye problems.

Conclusion The results of the present study revealed a high number of eye problems in children treated for ROP, emphasising the need for long-term follow-up. Retreatment of ROP was a risk factor for VI, and emphasises the importance of an accurate first treatment for the long-term ophthalmological outcome.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prematurely born children have more ophthalmological problems than children born at term.

WHAT THIS STUDY ADDS

⇒ This retrospective study was population-based and analysed the ophthalmological outcome at preschool age in all Swedish children treated for retinopathy of prematurity during 2007–2014. The study found that the degree of immaturity, as well as retreatment, was risk factors for ophthalmological problems.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study underlines the need for long-term follow-up of children treated for retinopathy of prematurity and the importance of an accurate first treatment at the correct time.

INTRODUCTION

Screening and treatment of retinopathy of prematurity (ROP) were introduced in the 1980s after the American cryotherapy multicentre study in which a favourable outcome was proven in treated eyes as compared with untreated eyes with threshold ROP.[1] Since then, the criteria for treatment have changed as well as the modality of treatment; that is, from cryotherapy to laser-treatment and nowadays also an injection of antivascular endothelial growth factor (anti-VEGF.)[2 3] Higher prevalence of refractive errors, strabismus and low vision have been reported in prematurely born children treated for ROP as compared with non-treated, as well as in children born extremely preterm without previous ROP.[4 5] Larger studies on treated children are however few.[6–8] In a web-based Swedish National Register for ROP registry, various data on screening and treatment for ROP, as well as on the ophthalmological outcome at around 6.5 years, are registered (2020).[9] The present study aims to report visual outcome, refraction and strabismus in a population-based cohort of children born 2005–2014 and treated for ROP in Sweden.

MATERIAL AND METHODS

The present study group included children born in Sweden between December 2005 and January 2014 and treated for ROP. The inclusion criterion for screening was initially gestational age (GA) <32 weeks and after revision of the guidelines in January 2012 <31 weeks.[10]

Detailed data on ROP and its treatment were retrieved from SWEDROP and ROP was classified according to the revised International Classification of ROP. Criteria for treatment followed the Early Treatment for Retinopathy of Prematurity

Cooperative Group recommendations (ETROP) and were performed in one of seven university hospitals.[11 12]

Neonatal data, such as GA (week+day), birth weight (BW) (grams), BW SD score (BWSDS) that represents the number of SD of individual weight below or above the mean BW taking into account sex and GA,[13] intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC) and pulmonary ductus arteriosus, are automatically imported to SWEDROP from the Swedish Neonatal Quality register. 'Neonatal brain lesion' was defined as IVH 3 or more and/or PVL. Data on cerebral lesions or general diseases later in childhood were not available.

According to Swedish guidelines, all treated children are annually followed up ophthalmologically through adolescence. The outcome of visual acuity (VA), strabismus and refraction at approximately 6.5 years is registered in SWEDROP by the local ophthalmologist.

'Better eye' was defined as the eye with the better VA. If VA was the same in the right (RE) and left eyes, the RE was registered as the better eye. If only binocular vision was assessed, that result was included among the better eyes when analysing VA.

VA had been performed with a logarithm of the minimal angle of resolution (logMAR) optotype chart and was noted as Snellen decimal acuity in the register. For further analyses in the study, logMAR values were used. In children who did not cooperate to the assessment with optotypes, preferential looking (PL) with Teller acuity cards or Cardiff cards were used together with the ability to fixate and follow or to perceive light.

The WHO defines mild visual impairment (VI) as VA over 0.3 logMAR and moderate VI as over 0.5 logMAR. Consequently, in the present study, 'minor VI' was defined as a VA >0.3 to 0.5 logMAR in the better eye and 'moderate VI' as a VA >0.5 logMAR in the better eye.

Only children who could cooperate at optotype assessment were included in analyses of mean and median values of VA. In analyses of VI, values from PL test were transformed to logMAR acuity,[14] and included in the different subgroups of no, minor and moderate VI. Ability to fixate and follow or of perception of light was included in the subgroup of VA >0.5 logMAR.

Refraction was performed during cycloplegia by retinoscopy or autorefraction. Cycloplegia was achieved by instilling a mixture of 0.85% cyclopentolate and 1.5% phenylephrine in the vast majority of the children. Spherical equivalent (SE) was calculated and astigmatism was noted. Anisometropia was defined as the difference of SE between the eyes. Refraction was analysed in better and worse eyes, as defined above. Significant myopia was defined as SE more than 3 dioptre (D), hypermetropia as SE more than 3 D, astigmatism as more than 2 D and anisometropia as more than 2D. 'Any refractive error' was defined as myopia more than 3 D and/or hypermetropia more than 3 D and/or astigmatism more than 2 D in the better eye and/or anisometropia more than 2 D.[5]

Strabismus was assessed with a cover-uncover test at distance and near. Stereopsis (yes/no) was measured by using TNO, Lang or Titmus tests.

'Any significant eye problem' was defined as VA >0.5 logMAR better eye and/or strabismus and/or 'any refractive error'.[5]

Statistical methods

Subject characteristics were presented as mean and SD, as well as range, for continuous variables and absolute and relative frequencies for categorical variables and for categorised continuous variables. Comparison of the effect of age at testing was performed using one-way analysis of variance for continuous variables and Fisher's exact test for categorical variables.

In order to evaluate prognostic factors for 'moderate VI', strabismus, hypermetropia SE more than +3D (better and worse eyes), myopia SE more than 3D (better and worse eyes), astigmatism more than 2D (better and worse eyes), anisometropia more than 2D, 'any refractive error' and 'any significant eye problem', stepwise logistic regression models adjusted for age were performed. In the models, gender, GA at birth, BW, BWSDS, NEC (yes/no), BPD (yes/no), 'neonatal brain lesion' (yes/no), retreatment (yes/no) and PMA and PNA at first treatment were included as independent variables and the optimal model was determined based on Akaike information criterion. No adjustment for multiplicity has been performed and thus the results should be interpreted with that in mind. A $p<0.05$ was regarded as significant.

RESULTS

During the study period, 270 infants treated for ROP were registered in SWEDROP. Follow-up data were registered in 232 children, 140 boys (60.3%) with a median age of 6.5 years. In the drop-out group, 11 children had died, 4 had emigrated and 23 were lost to follow-up.

The purpose of the present study was to gather data at an age of 6.5±1 year. Of the 232 children, 194 were examined at this age, 22 below 5.5 years and 16 over 7.5 years. Descriptive data are presented in table 1.

There were no statistical differences between the study group and the drop-out (38) group regarding gender, neonatal data, number of treatments, PNA or PMA at first treatment.

The maximum stage of ROP in the neonatal period was ROP stage 3 in 214 children, stage 4A in 7, stage 4B in 3 and stage 5 in 8 children.

In 91 children, the type of ROP was unknown. Type 1 ROP was fulfilled in 114 of the REs and in 111 of LEs. In either eye, type 1 was fulfilled in 120/141 (85.7%) children.

Treatment was performed in 99.1% (230/232) of the REs and in 98.7% (229/232) of the LEs.

Postnatal age and PMA at first treatment are given in table 1.

Of the 232 children, 156 (67.2%) had received 1 treatment, 55 (23.7%) 2, 17 (7.3%) 3, 2 (0.9%) 4 and 2 (0.9%) 5 treatments in either or both eyes, see table 2. In five children only one eye was treated. Altogether, retreatment was performed in 71/230 (30.8%) REs and in 69/229 (30.1%) LEs.

Retreatment was correlated to PNA and PMA at first treatment in univariate analyses, but in the multivariable analysis, PNA was the only risk factor. Every additional week of PNA reduced the risk for retreatment (OR 0.81, 95% CI 0.71 to 0.91, $p=0.001$). The prevalence of retreatment differed between the seven treating centres ($p<0.001$), ranging from 2/67 (2.99%) to 34/56 (60.7%), as did the mean values of GA (24.26 to 25.88 w ($p=0.002$)) and BW (615 to 761 g ($p=0.005$)).

Laser therapy alone was performed in 207 REs and 210 LEs, anti-VEGF injections only in 4 REs and 4 LEs and cerclage only in 1 RE and 1 LE. The remaining eyes had a combination of treatments (see table 2).

As primary treatment, laser alone was given in 223 REs and 219 LEs (table 2), of which 69 (30.9%) REs and 65 (29.6%) LEs were retreated.

Six REs and LEs were given anti-VEGF as the first treatment, of which two REs and LEs needed retreatment.

Table 1 Descriptive data of 232 children treated for ROP during 2007–2014 and registered in the Swedish national quality register for ROP

Sex	N (%)	
Girl		92 (39.48)
Boy		140 (60.32)
Age at examination (year)	Mean (SD)	6.57
	Median	6.5
	Range	2.8–12.3
GA at birth (week)	Mean (SD)	24.97 (1.63)
	Median	24.71
	Range	22.0–30.14
BW (gram)	Mean (SD)	699 (175)
	Median	668
	Range	400–1230
BWSDS	Mean (SD)	−0.34 (0.85)
	Median	−0.25
	Range	-2.6-1.4
BPD	N (%)	
Yes		159 (68.53)
No		73 (31.47)
NEC	N (%)	
Yes		44 (18.97)
No		188 (81.03)
Brain lesion	N (%)	
Yes		32 (13.79)
No		200 (86.21)
Maximum no of treatments	Mean (SD)	1.44 (0.74)
	Median	1
	Range	1-5
PNA at first treatment	Mean (SD)	12.87 (2.90)
	Median	12.43
	Range	7.0–25.57
PMA at first treatment	Mean (SD)	37.85 (3.13)
	Median	37.14
	Range	32.43–52.14

Brain lesion defined as intraventricular hemorrhage ≥3 and/or periventricular leukomalacia.
BPD, bronchopulmonary disease; BW, birth wt; BWSDS, birth weight SD score; GA, gestational age; NEC, necrotising enterocolitis; n, number; PMA, postmenstrual age; PNA, postnatal age; ROP, retinopathy of prematurity.

Altogether, 17 REs and 14 LEs were treated with anti-VEGF at any time (table 2). Three REs and LEs, respectively, were given ranibizumab and 14 REs and 11 LEs bevacizumab.

VA or visual behaviour

VA or behaviour was measured in 225 of 232 children, 3 children could not cooperate at all and four children lacked data on VA. Optotype VA was measured in 204 children. PL tests were used in eight children. In two of these the converted values in better eyes were ≤0.3 logMAR acuity, two had a converted value between >0.3 and 0.5 logMAR, and four children had a value >0.5 logMAR. Seven children could only fixate and follow, four had perception of light and two had no perception of light in any eye.

Mean and median values of logMAR VA in better and worse eyes in children assessed with optotypes together with the prevalence of VI (minor and moderate) in better eyes are presented given in table 3. Altogether, 32/225 (14.2%) children had VI according to WHO's definition (>0.5 logMAR).

In a multivariable analysis of moderate VI adjusted for age at examination, retreatment was the only risk factor with an OR of 3.49 (95% CI 1.55 to 7.88, p=0.003).

The visual outcome of the 18 children with ROP stage 4–5 is presented in online supplemental eTable 1.

Strabismus

Strabismus was found in 82 (38.1%) of 215 examined children. Type of strabismus is given in online supplemental eTable 2. In a multivariable regression analysis adjusted for age, boys had higher risk (OR 2.13, 95% CI 1.16 to 3.92, p=0.015) for strabismus together with the children with neonatal brain lesion (OR 2.32, 95% CI 1.03 to 5.24, p=0.043). Each additional week of GA lowered the risk of strabismus (OR 0.79, 95% CI 0.65 to 0.95, p=0.014).

There was no stereopsis in the 82 children with strabismus or in 18 of the children without strabismus.

Refraction

The refraction was measured in 218 and 217 REs and LEs. Figures 1 and 2 show the SE and astigmatism values as well as hypermetropia, myopia, astigmatism and anisometropia in better and worse eyes. The anisometropia could be calculated in 211 eyes and revealed a mean value of 1.50D (SD 2.22) (median 0.625 D (range 0–14.0)). Altogether, 'any refractive error' was found in 114/217 (52.5%) children.

Results of multivariable analyses of refractions are summarised in online supplemental eTable 3.

'Any significant eye problem' was found in 143/220 (65.0%) children. In a multivariable logistic regression analysis adjusted for age, every additional week of gestation and of PNA at first treatment reduced the risk (GA at birth: OR 0.79, 95% CI 0.66 to 0.95, p=0.013; PNA: OR 0.88, 95% CI 0.79 to 0.98, p=0.019) of significant eye problems.

Of the 32 children with VI according to WHO's definition, 21 children (66%) had strabismus. The children with VI were more myopic both in better (p<0.001) and worse eyes (p<0.001) than those with VA ≤0.5 logMAR. Eleven of the 32 children had ROP stages 4–5, of which 7 in both eyes and 1 had macular scaring in both eyes. Twenty-two (68.8%) children had been treated 2–5 times. Six children had neonatal brain lesions and another two had optic atrophy at follow-up.

There were no statistical differences between the different age groups (<5.5 years, 5.5–7.5 years, >7.5 years) in any of the different follow-up analyses.

DISCUSSION

In the present Swedish, retrospective population-based study of children treated for ROP between 2007 and 2014, VI (VA <0.3) was found in 14.2%, strabismus in 38.1%, refractive error in 52.5% and any significant eye problem in 65.1% of the children. Retreatment for ROP was the only risk factor for VI. Further, retreatment was associated with lower PNA at treatment as well as treatment sites. Retreatment was also associated with refractive error, and each additional week of GA reduced the risk for refractive errors. Male sex and neonatal brain lesions were risk factors for strabismus while each additional week of age of GA reduced the risk. Further, each additional postnatal week of age at first treatment as well as each additional week of GA reduced the risk for any significant eye problem.

Table 2 Number and type of treatments in the 232 (230 RE and 229 LE) children treated for ROP

	RE	LE			
	N=232	N=232	Type of treatment		
No treatment	2 (0.9%)	3 (1.3%)		RE	LE
One treatment only	159 (68.5%)	160 (69.0%)	Laser	154	154
			Anti-VEGF	4	4
			Cerclage	1	1
			Laser/cryotreatment		1
Two treatments	54 (23.3%)	50 (21.6%)	Laser+laser	48	48
			Laser+anti-VEGF	3	1
			Laser+laser/anti-VEGF	2	
			Laser+cerclage	1	
			Cryotreatment+laser/anti-VEGF		1
Three treatments	14 (6.0%)	17 (7.3%)	Laser x 3	5	7
			Laser x 2+anti-VEGF	1	2
			Laser+anti-VEGF+laser	1	
			Laser x 2+cryotreatment	1	1
			Laser x 2+cerclage		1
			Laser x 2+vitrectomy	1	
			Laser x 2+vitrectomy/anti-VEGF		1
			Laser+anti-VGEF+laser		1
			Laser+cryotreatment+anti-VEGF	1	1
			Laser+antiVEGF +Vitrectomy	1	
			Laser+Vitrectomy+Lensectomy/anti-VEGF	1	
			Anti-VEGF x 2+Laser	2	2
			Cryotreatment+anti-VEGF+vitrectomy		1
Four treatments	1 (0.4%)	2 (0.9%)	Laserx3+cerclage		1
			Laserx3+vitrectomy	1	
			Laserx2+cerclage+vitrectomy/lensectomy		1
Five treatments	2 (0.9%)	0	Laserx3+antiVEGF+cerclage	1	
			Laser x 3+cerclage+evisceration	1	

LE, left eye; RE, right eye; VEGF, vascular endothelial growth factor.

There are numerous studies on the short time outcome of different treatment modalities for ROP. Likewise, there are studies on ophthalmological outcomes in preterm infants from childhood up to adulthood, including both treated and untreated individuals, revealing the highest risk for visual and ophthalmic sequelae in individuals treated for ROP.[5 15–17] Large follow-up studies in children treated for ROP are, however, few. The ETROP study reported the follow-up at 3–6 years of age.[6 18] The BEAT-ROP and Rainbow studies, in which laser treatment and injection of anti-VEGF were compared, presented the outcome at 2–3 years of age.[7 8] Further, the EXPRESS study, reported the ophthalmological outcome at 6.5 years in Swedish children born before 27 weeks of gestation, including 84 children treated for ROP.[5]

Table 3 Visual acuity (VA), expressed as logMAR, in better and worse eyes, together with the prevalence of visual impairment in the study group of children treated for ROP

VA better eye/binocular*	Mean (SD)	0.23 (0.24)
	Median	0.16
	Range	0–1.49
	N	204
VA worse eye*	Mean (SD)	0.36 (0.36)
	Median	0.22
	Range	0–1.7
	N	185
Visual Impairment†	N (%)	
None: ≤0.3		167 (74.2)
Minor: >0.3 to 0.5		26 (11.5)
Moderate: >0.5		32 (14.2)

*Only VA assessed with optotype included.
†In 225 of 232 children.
logMAR, logarithm of the minimal angle of resolution; ROP, retinopathy of prematurity.

The prevalence of VI in the present study was lower than in the ETROP study, in which approximately 50% of the children had a VA above 0.5 logMAR at the age of 6 years vs 14.2% in the present study.[6] The great difference is hard to explain since treatment criterion was the same and most of the children in our cohort were treated with laser as in the ETROP study. However, in the present study, type 1 ROP was not fulfilled in 15%, indicating that some of the children were treated at an earlier stage which might result in a better outcome. The prevalence of VI was high compared with a general population of Swedish children (0.1%)[19] and to other cohorts of preterm children including also children not treated for ROP.[5 16]

Advanced ROP is an important risk factor for VI, which was confirmed in the present study where 8 of 10 eyes with ROP stage 5 had no perception of light and 4 of 5 eyes with ROP stage 4B had a VA more than 1.0 logMAR (see online supplemental eTable 1). Among 10 eyes with ROP stage 4A, only 2 had VA≤0.5 logMAR (0.5 and 0.4, respectively).

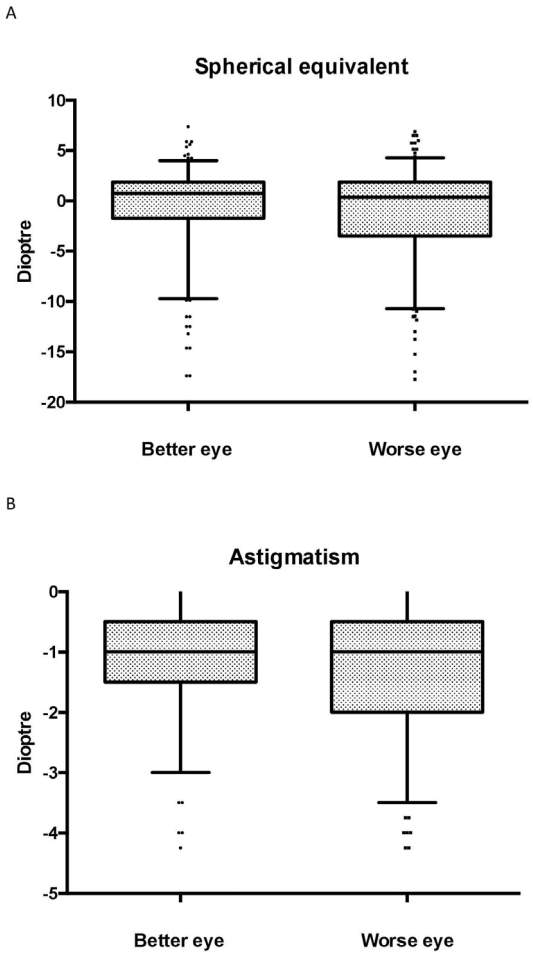

Figure 1 Boxplots of spherical equivalent (A) and astigmatism (B) in better (218) and worse (211) eyes in children treated for retinopathy of prematurity. The horizonal lines represent the median values, boxes the IQR and whiskers 5–95 percentiles.

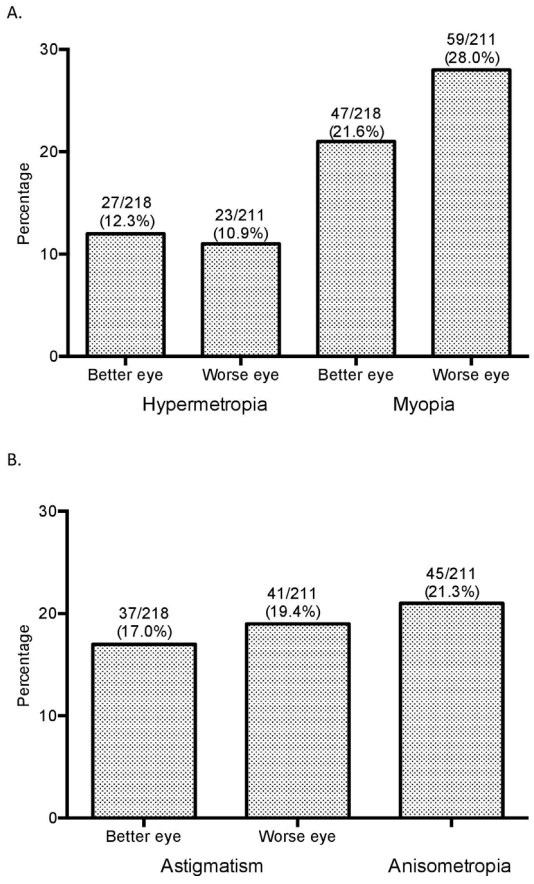

Figure 2 (A, B) The prevalence of hypermetropia, myopia, astigmatism in better and worse eyes together with anisometropia in children treated for retinopathy of prematurity. The percentage on the y-axis and number above the bars. Significant hyperopia was defined as spherical equivalent (SE) more than 3D (D), myopia SE more than 3D, astigmatism as more than 2D and anisometropia as more than 2D.

In the present study, we did not have information on the neural imaging or the neurological outcome and thus, we cannot with certainty explain the aetiology of the VI in each child. Nevertheless, we estimated that in at least 12 of the 32 children the VI had retinal causes and in at least 7 children the causes were neurological.

The prevalence of strabismus in the present study (38%) was similar as among treated children in the Swedish Express study (34%) and as in the ETROP study (42%) at 6 years of age.[5 6]

The definition of refractive errors of the present study, as well as age at the examination, was the same as in the EXPRESS study.[5] Among the 84 treated infants in the EXPRESS study, prevalences of hypermetropia, myopia and astigmatism were similar to the present study, while anisometropia (32%) was more common in the EXPRESS cohort than in our study (21%) (figure 2A,B). Regarding astigmatism, our results accorded with the ETROP study and a study by Fledelius *et al*, although the children were younger in the latter studies.[16 18] In the Beat-ROP study at 2.5 years, children treated with laser had higher myopia than children treated with anti-VEGF.[7] In the present study, however, in which most of the children were treated with laser, myopia was much lower (figure 1). The Rainbow study also reported a higher prevalence of myopia more than 5.0D at 2 years of age in 20% of children treated with laser, as compared with 14.2% (31/218) in better eyes of the present study, although examined at a higher age.[8]

The present study revealed some kind of significant eye problems in almost two-thirds (65%) of the children as opposed to 6.2% of a control group of 300 children born at term and included in the EXPRESS study, emphasising the need for regular ophthalmic follow-up of children treated for ROP. As expected, the risk for problems was most pronounced in the most prematurely born children as well as in those treated at an early postnatal age, reflecting the earlier onset and/or the more pronounced severity of ROP in the most immature children.

In the current study, retreatment was a risk factor for both VI and refractive errors. Further, there was a difference in retreatment frequency among the seven treatment centres, which accorded with a study by Lundgren *et al* who analysed all Swedish infants born before 24 weeks of GA, during 2007–2018 registered in SWEDROP.[20] In the present study, however, GA at birth and BW differed between the centres, and we cannot conclude whether the retreatment frequency reflects differences in immaturity of the infants and/or differences in treatment techniques. Nevertheless, this finding emphasises performing an accurate first treatment at the correct time to avoid the necessity of retreatment.

Strengths and limitations

The limitation of the study was that it was retrospective, including data on children treated for ROP and retrieved from our national register for ROP. Around 95% of the children were primarily treated with laser, but only six children received anti-VEGF injections as

primary treatment, making it impossible to conclude the outcome of the two primary treatments. Further, there was no control group of children born at term. In addition, we had no information about visual perception, neurological imaging and/or paediatric examinations, which would have helped to explain VI in some of the children.

The strength of the present study was that it was population based, covering the whole country and with a drop-out rate of only 14%. Data had been retrieved from a national ROP register with a coverage of around 98% and including neonatal information on various aspects of ROP and of the eventual treatment, as well as some major neonatal data imported from a Swedish neonatal register.

To summarise, the present study showed that 14% of children treated for ROP had VI according to WHO and 65% of the children had some kind of significant eye problem. The results underline the need for long-term follow-up of children treated for ROP to provide them with adequate glasses, eventual occlusion therapy and referral to the low-vision centre for visual habilitation when needed.

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eTable 1. The outcome (visual acuity (VA), refraction and retinal outcome) in 18 children with ROP stage 4-5 in one or two eyes. Neonatal data and number of treatments included in the table.

	Max ROP RE / LE	**Neonatal data**	**PNA at first treatment**	**Right eye**	**Left eye**
1	3 / 5	GA 25+4 w BW 830 g BWSDS 0.2 Boy	11 w	VA: 0.4 logMAR +3.0 2 treatments	VA: LP Total detachment 1 treatment
2	5 / 3	GA 23+3 w BW 585 g BWSDS -0.2 Boy	19 w	No LP Total detachment 2 treatments	VA: 0.8 logMAR -9.9 D Dragged vessels 2 treatments
3	5 / 4B	GA 25+2 w BW 635 g BWSDS -1.0 Girl	12 w	VA: 1.0 logMAR -9.6 D 2 treatments	VA: 0.8 logMAR -12.5 D 2 treatments
4	3 / 5	GA 25+0 w BW 770 g BWSDS 0.2 Girl	12 w	Fixate and follow -13 D 2 treatments	No LP Total Detachment 1 treatment
5	3 / 5	GA 24+2 BW 756 BWSDS Boy	13 w	VA: 0.2 logMAR -1 D 4 treatments	No LP Total detachment 3 treatments
6	5 / 5	GA 24+3 w	11 w	No LP	No LP

		BW 637 g BWSDS 0.7 Boy		Total detachment 2 treatments	Total detachment 4 treatments
7	5/5	GA 29+4 w BW 1200 g BWSDS -0.4 Boy	7 w	No LP Total detachment Cataract 3 treatments	No LP Total detachment 3 treatments
8	5 / 3	GA 24+4 w BW 784g BWSDS Boy	10 w	No LP 5 treatments	VA: 0.8 logMAR ± 0 D Dragged vessels 4 treatments
9	4B / 4B	GA 22+1 w BW 490 g BWSDS 0.7 Girl	19 w	LP Total detachment 2 treatments	LP Partial detachment 2 treatments
10	3 / 4B	GA 25+5 w BW 870 g BWSDS 0.4 Boy	10 w	VA: 0.3 logMAR -4.5 D 3 treatments	VA: >1.0 logMAR -5.0 D Dragged vessels 3 treatments
11	4A / 4B	GA 24+0 w BW 670 g BWSDS 0.2 Boy	12 w	No fixation 3 treatments	VA: 1.5 logMAR -0.38 D 3 treatments
12	4A / 3	GA 27+1 w BW 934g BWSDS -0.2 Boy	15 w	VA: 1.0 logMAR -13.75 D 1 treatment	VA: 0.3 logMAR +0.25 D 0 treatment
13	4A / 3	GA 23+3 w BW 565 g	12 w	VA: 0.4 logMAR -2.125 D	VA: 0.4 logMAR -2.0

		BWSDS -0.4 Girl		1 treatment	1 treatment
14	4A / 4A	GA 27+1 w BW 1039 g BWSDS 0.4 Girl	14 w	VA: >1.0 logMAR +3.0 D Dragged vessels 2 treatments	VA: 0.7 logMAR +1.0 D Dragged vessels 2 treatments
15	3 / 4A	GA 25+2 w BW 782g BWSDS 0.1 Boy	10 w	VA: 0.9 logMAR -2.0 D Dragged vessels 2 treatments	VA: 0.9 logMAR -2.375 D Dragged vessels 2 treatments
16	4A / 4A	GA 22+5 w BW 533 g BWSDS -0.2 Girl	10 w	VA: 1.0 logMAR No data 3 treatments	VA: 0.5 logMAR -9.25 D 1 treatment
17	3 / 4A	GA 24+5 w BW 470g BWSDS -2.0 Girl	8 w	Fixate and follow binocular -13.0 D ONH 3 treatments	-10.375 D 3 treatments
18	4A / 3	GA 24+0 w BW 623 g BWSDS -0.3 Girl	10 w	No perception Detachment 5 treatments	VA: 0.9 logMAR -9.0 D Macular scarring 3 treatments

D=dioptres, LE=left eye, LP=light perception Max=maximum, PNA= postnatal age, ONH=optic nerve hypoplasia, RE= right eye, ROP=retinopathy of prematurity, VA= visual acuity, w = weeks

eTable 2. Type of strabismus in 82 of 215 children in which strabismus was assessed.

Type of strabismus	**Number**
Esotropia distance and/or near	59
Exotropia distance and/or near	16
Exotropia distance, Esotropia near	2
Vertical distance and near	1
Esotropia/vertical distance and/or near	2
Unknown	3

eTable 3. Statistically significant results of multivariable regression analyses of refraction performed after adjustment of age

	Odds Ratio	**95% CI**	**P-value**
Hypermetropia better eye			
Retreatment	0.25	(0.07-0.90)	0.033
Myopia better eye			
Retreatment	4.6	(2.31-10.43)	<0.001
Myopia worse eye			
Sex (boys vs girls)	2.24	(1.08-4.64)	0.03
BW (increase 100 g)	0.73	(0.54-0.97)	0.031
Astigmatism better eye			
Retreatment	4.34	(2.04-9.26)	<0.001
Anisometropia			
GA at birth	0.67	(0.51-0.86)	0.002
Any refractive error			
GA at birth	0.73	(0.61-0.89)	0.001
Retreatment	2.57	(1.31-5.06)	0.006

Hypermetropia defined as spherical equivalent (SE) more than 3 dioptres (D), Myopia defined as SE more than 3 D, astigmatism defined as more than 2 D, anisometropia defined as more than 2 D
Any refractive error defined as hypermetropia more than 3 D and/or Myopia more than 3 D and/or astigmatism more than 2 D in the better eyes and/or anisometropia more than 2 D.
CI=confidence intervals