Retinopathy of prematurity in the period 2015-2019 in a tertiary referral centre in Slovenia

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Abstract

Background: Retinopathy of prematurity (ROP) is the leading cause of blindness among prematurely born children. The incidence of any stage of ROP in children born before the 31st gestational week in Europe and the USA is between 10-45%. The purpose of this study was to show characteristics of ROP between 2015 and 2019 at the Neonatal Intensive Care Unit of the University Medical Centre Ljubljana (NICU-Lj), which is the larger of the two tertiary referral centres in Slovenia and in which more than two thirds of Slovenian very low birth weight children are treated.

Methods: All prematurely born children screened for ROP at NICU-Lj between 2015 and 2019 were included in the study. The following parameters were recorded: number of children screened, total number of exams, number of exams per child, number of children with ROP, ROP stages, number of children who needed ROP treatment and number of treatments per child treated.

Results: Between 2015 and 2019, 82-130 prematurely born children fulfilled ROP screening criteria each year. A total of 1,412 exams were performed over the period of five years (range: 239-386 per year). Every child had one or more ROP screening exams (range: 1-10). Extremely preterm children born before the 27th week of gestation had more exams (average: 5 exams/child) compared to other prematurely born children (average: 1.5 exams/child). The number of prematurely born children with any stage of ROP ranged from 17 to 30 per year. ROP of any stage was present in 18.75% (2015), in 17.7% (2016), in 23% (2017), in 29.3% (2018), and in 24.1% (2019). More than 70% of all babies with ROP were born before the 27th gestational week. The most mature baby with ROP was born with 29 6/7 weeks of gestational age. Every year, 15-35% of babies with ROP received laser treatment.

Conclusions: ROP is an important disease in prematurely born children. During the period 2015-2019, the incidence of any stage of ROP and of serious ROP requiring treatment was comparable. The screening and treatment of ROP requires intense cooperation between paediatric ophthalmologists and neonatologists in order to prevent blindness in prematurely born children.
1 Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative vitreoretinal disease affecting preterm babies, which was first described in the 1940s as retrolental fibroplasia (1). The first “epidemic” of ROP was associated with uncontrolled oxygen supplementation in a growing population of prematurely born children in industrialized countries (2). Later on, a better balance between ROP incidence and oxygen supplementation was achieved, but in high-income countries a “second epidemics” of ROP is taking place due to advances in neonatal care and an improved survival rate of more immature and sicker babies (3).

The incidence of any stage of ROP in preterm babies born prior to the 31st gestational week in Europe and the USA is reported to be between 10% and almost 45% (4-6). In Slovenia, ROP did not seem to be an epidemiological problem in the years 1990-1999, when any stage of ROP was reported in only 50 babies out of more than 1300 screened (about 3.8%) (7).

Revised criteria from 2005 are still valid for ROP classification (8). ROP can be classified according to the location of the disease into zones I-III, according to the extent of the disease expressed as clock hours or as 30° sectors, and according to the disease severity into 5 stages. Stage 1 is characterized by the demarcation line, stage 2 by the ridge, stage 3 by extraretinal fibrovascular proliferation, stage 4 by partial retinal detachment, and stage 5 by total retinal detachment. There are separate signs indicating ROP severity such as PLUS and pre-PLUS disease, mainly describing venous dilatation, arterial tortuosity, iris vascular engorgement, poor pupillary dilatation and vitreous haze. Definitions are summarized in Table 1.

A rare but very important form of rapidly progressing ROP called aggressive posterior ROP (AP-ROP) is characterized by increased dilatation and tortuosity of posterior pole vessels in all 4 quadrants that is out of proportion to the peripheral retinopathy (8). ROP that would in 50% of cases progress to retinal detachment if left untreated was defined as threshold ROP (Zone I or II with PLUS disease and 5 contiguous or 8 total clock hour sectors of stage 3), which needs treatment within 72 hours (9). Pre-threshold ROP is defined as Zone I of any stage of ROP or Zone II stage 2 with PLUS disease or Zone II stage 3 without PLUS disease or Zone II stage 3 with PLUS disease and less than threshold (10). Type I ROP is defined as high risk pre-threshold ROP (Zone I any stage with PLUS disease or Zone I stage 3 without
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Type 2 ROP is defined as low-risk pre-threshold ROP (Zone I, stage 1 or 2 without PLUS disease, Zone II stage 3 without PLUS disease) and requires close monitoring (11). In Slovenia, prematurely born children of less than 31 weeks of gestational age and/or of less than 1,500 g birth weight (very low birth weight infants, VLBWI) are screened for ROP by paediatric ophthalmologists. The first exam is usually performed within the 30th gestational week and then repeated exams follow depending on the ROP presence or absence and of ROP status, but usually every 1-2 weeks for about 6-10 weeks. Babies with significant ROP and those needing treatment are followed very closely, usually every 2-3 days. The exam of the back of the eye is performed by indirect ophthalmoscopy in previously dilated pupils. Lenses 20D, 28D or 40D are used to visualise the retina.

The standard treatment for severe ROP is diode laser photocoagulation of the avascular retina in order to minimize vascular endothelial growth factors (VEGF) causing vascularized retina to detach. A laser is applied through the diluted pupil to the retina. The laser treatment is performed under general anaesthesia and usually takes 1-2 hours per procedure. Known side effects of laser photocoagulation of peripheral retina include peripheral visual field constriction and higher myopia. Another option of treatment, reserved for special situations such as AP-ROP, very sick babies who do not tolerate the general anaesthesia, etc. is anti-VEGF drug delivered intravitreally as injection. This second option is very appealing since it requires minimal skill, it only takes a few minutes and the baby does not require general anaesthesia. However, babies treated with anti-VEGF drugs require much longer follow-up, since ROP recurrences are more often present months or even years after the treatment (12). The systemic influence of anti-VEGF drugs is also not clear yet and there is growing evidence that children who were treated with anti-VEGF achieve lower neurodevelopmental scores than those treated with laser only (13).

The purpose of this study was to show characteristics of ROP between 2015 and 2019 in the Neonatal Intensive Care Unit at the University Medical Centre Ljubljana (NICU-Lj), which is the larger of the two tertiary referral centres in Slovenia and in which more than two thirds of all children with very low birth weight are treated.

## 2 Children and methods

The screening protocol for ROP included all babies born before the 31st gestational week (GW) and with a birth weight (BW) of less than 1500g. The first eye exam was performed at 31st week postmenstrual age in infants with a gestational age of <27 GW at birth, and at four weeks chronological age in infants with gestational ages of >27 GW at birth. Screening for ROP was performed according to the screening protocol using indirect ophthalmoscopy, with maximal pupillary dilatation; indentation of the sclera was utilized to visualize peripheral retina if needed (14) by a skilled paediatric ophthalmologist.

Children were divided into three groups: (1) born before the 27th GW, (2) born before the 31st GW with BW < or >1500 g, and (3) born after the 31st GW, BW <1500 g. The following parameters were recorded for each group and for each year: number of children screened, total number of exams, number of exams per child, number of children with ROP, ROP stages, number of children who needed ROP treatment and number of treatments per child treated.

The results are shown as absolute numbers (for number of children, number of exams, number of children with ROP and number of children treated for ROP) or as mean values (for number of exams per child). Shares are shown as percentages.

The study was approved by the Committee for Medical Ethics of the Republic of Slovenia on April 2018 (decision no. 0120–249/2018/4).
3 Results

Between 2015 and 2019, each year 82-130 prematurely born children fulfilled ROP screening criteria in the NICU-Lj. A total of 1,412 exams were performed by paediatric ophthalmologists over the period of five years (ranging from 239 to 386 per year). The data are presented in Figure 1.

Every prematurely born child had one or more ROP screening exams, ranging from 1- to 10 exams. Extremely preterm children (born <27th GW) had more exams compared to other prematurely born children. Data for the period 2015-2019 period are presented in Figure 2.

The number of prematurely born children with any stage of ROP ranged from 17 to 30 a year. ROP of any stage was present in 18.75% of babies screened in 2015, in 17.7% in 2016, in 23% in 2017, in 29.3% in 2018, and in 24.1% in 2019. The data for each year are presented in Figure 3.

Each year more than 70% of all babies with ROP were born before the 27th gestational week. The data are presented in Figure 4.

The majority of ROP regressed spontaneously without treatment, but 15-35% of babies with ROP received laser treatment every year. The data are presented in Figure 5.

Most babies with ROP needed only one diode laser treatment. However, there were 2 children in 2017 and one child in 2018 and in 2019 who needed a second laser treatment.

Between 2015 and 2019, there were two children with ROP progression to partial or total retinal detachment despite treatment. Both were extremely preterm. The first boy was born in the 23rd GW and the second in the 24th GW. Both of them had other prematurity related co-morbidities such as bronchopulmonary dysplasia, bacterial infections, and necrotizing enterocolitis.

4 Discussion and conclusions

This single tertiary referral centre (Neonatal Intensive Care Unit at of the University Medical Centre Ljubljana, NICU-Lj) retrospective study has shown major characteristics of retinopathy of prematurity (ROP) between 2015 and 2019. ROP of any stage was present on average in 22% of the children screened, however, serious ROP requiring treatment was present on average in 5.6% of the children screened. The results are in accordance with a similar cohort study from the UK, where a 7-year mean of 8.2% of all babies screened needing treatment was reported (15). However, in a much larger multicentre US study, 40% of screened babies developed some stage of ROP and approximately 12.5% developed severe ROP (6).
An increase in ROP in NICU-Lj between the last published data (1990-1999), when only 3.8% of any stage ROP was reported (7) and the present study is observed. A similar pattern was reported from a comparable tertiary referral centre in Zurich, where an increased ROP incidence was observed since mid-2015. Increased survival rate was found to be the only causative factor in Zurich NICU (16). The survival rate of very prematurely
born children has also increased in at the University Medical Centre Ljubljana during the last two decades; 29 children born before the 27th GW survived in 1998 (0.51% of all live births), 38 children in 2008 (0.56% of all live births), and 39 children in 2018 (0.67% of all live births). An important difference was noted in the ROP screening protocol between the periods of 1990-1999 and 2015-2019 in the NICU-Lj, namely the use of indirect
ophthalmoscopy as the golden standard for screening prematurely born children for ROP. The direct ophthalmoscope, which gives limited visibility of the retinal periphery, was still used in the period 1990-1999.

A great majority of prematurely born children in the present cohort who developed severe ROP were extremely preterm. Among 28 children who were treated for ROP during the period 2015-2019, there was only one girl born after the 27th GW, all the others had lower gestational age. There are other studies reporting an increased incidence of ROP requiring treatment among very preterm infants (15,17).

Until now, the ROP screening criteria for preterm babies in Slovenia were in accordance with the screening criteria in other high-income countries (14,18). The present study has shown that only 15% of all babies (17/109) with any stage of ROP were born after the 27th GW and among them only one child developed serious ROP requiring treatment. Moreover, no ROP cases were documented in babies born after the gestational age of 29 GW and 6 days. The question whether to change the screening criteria in order to decrease the number of infants who need examination while maintaining high sensitivity for detection of those with a high risk of severe ROP development has already been raised by the G-ROP study group (19). The study has shown that besides gestational age and birth weight the most important prediction factor for severe ROP development was postnatal weight gain. The weight gain data were unfortunately not available for the present cohort of prematurely born children.

ROP stage 1-2 in anterior zone II and in zone III were the most common forms of ROP every year during the 2015-2019 period. In the great majority of eyes, ROP did not progress. However, in the NICU-Lj, the aggressive posterior ROP (AP-ROP) was first described in 2016. In the following years, there were 1 or 2 extremely preterm babies with this form of ROP every year. All of AP-ROP eyes required treatment, which is in accordance with previous findings (8). The AP-ROP was introduced into ROP screening guidelines in 2005, where it was described as a more virulent ROP form in the tiniest babies and as such it was recognized as a diagnostic entity (8). Since then, it is well known that if left untreated, AP-ROP usually progresses to total retinal detachment, and also that despite early and aggressive treatment favourable outcome is expected in only around 75% of eyes with AP-ROP (20). In the present study ROP progressed into total retinal detachment in 2 babies, they both had AP-ROP and were extensively treated with laser or with a combination of anti-VEGF and laser.

The majority of children with severe ROP requiring treatment were treated only with diode laser photocoagulation, which is still the golden standard of treatment (21). In four babies only one laser treatment was not sufficient, since the ROP did not regress completely. An additional laser treatment was performed. In a few of very sick children, anti-VEGF drug was given intravitreally prior to laser treatment. However, anti-VEGF drugs were off-label drugs until recently. There are still unknown systemic effects of these drugs on the developing body and there is growing evidence of higher neuro-developmental impact of these drugs than it was previously thought (13).

The major limitation of the present study is the inclusion of only one national tertiary referral centre. Some extremely preterm babies in Slovenia are treated for ROP in the other NICU in Maribor. According to the National Perinatal Information System of Slovenia (national register) (22) an average of 15% of all prematurely born children with gestational age <27 weeks are born in Maribor. However, the published data on ROP in Maribor were not available for the present study.

To conclude, the present study has given an insight into ROP characteristics during the last five years in the NICU-Lj. The increase of ROP incidence since the last published data (1990-1999) was well documented. The authors believe the main reason lies in the increased survival rate of extremely preterm and sick babies, but to minor extend however also in the standardized screening protocol with the use of indirect ophthalmoscopy and documentation of any stage of ROP. The appearance of AP-ROP in very preterm and sick children was also described. A joint effort of paediatric ophthalmologists and neonatologists is crucial in detecting, staging and treating ROP and thus saving preterm children from blindness.

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Conflict of interest

None declared.
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