Four Years Experience in Retinopathy of Prematurity

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Purpose: Analysis of the results of screening and treatment for retinopathy of prematurity (ROP) in a sample of prematurely born babies evaluated in the Neonatal Intensive Care Unit and Neonatology Prematures Clinic of Targu Mures, between January 2008 and January 2012.
Material and method: We conducted a prospective study on all premature infants born with less than 34 weeks gestational age (GA) and lower than 2000 g birth weight (BW). The first ophthalmoscopic examination was performed between 4 and 6 weeks after birth, regardless of gestational age. The treatment was needed in threshold (or prethreshold) disease.
Results: Different stages of ROP were found in 24.1% from the total 503 infants: stage 1 in 34 eyes (28.1%), stage 2 in 65 eyes (53.7%), stage 3 in 16 eyes (13.2%) and stage 5 in 6 eyes (5%). We didn't have cases with stage 4 ROP. Statistical analysis showed that GA and BW are highly significant risk factors for the development of ROP, with a risk reduction as the values of gestational age and birth weight were higher. The indication for laser treatment was set at 3.97% of all premature, respectively in 16.53% of children with ROP. Favorable evolution after laser treatment was observed in 80% of cases. From the others, who had no positive response to laser treatment, 75% had aggressive posterior ROP (APROP). We recorded a statistically significant association between BW and the incidence of cases which required laser therapy (p=0.0058), but no statistically association was found between GA and grades of diseases that needed laser (p=0.0789).
Conclusions: Screening for retinopathy of prematurity requires an experienced paediatrician-ophthalmologist, recognition of severe disease that requires treatment being crucial. Performed strictly and in accordance with international protocols, screening remains the first step in the detection and management of retinopathy of prematurity.

Keywords: retinopathy of prematurity, premature infants, laser therapy

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Introduction

Screening for retinopathy of prematurity is one of the most important objectives in paediatric ophthalmology worldwide, because of potential risk of blindness. Therefore, it is mandatory to detect retinopathy of prematurity and to monitor disease in order to find the best time for therapeutic intervention. Likewise, proper follow-up to detect late complications is required.

Retinopathy of prematurity is divided into five stages of severity (1–5) and into three zones of location (I–III). The plus disease, considered as a sign of serious illness, consists in tortuosity and dilation of the posterior pole vessels, the engorgement of iris vessels or cloudy vitreous aspects.

The aggressive posterior ROP, sometimes referred to as "Rush disease", is the most severe form of ROP and has the following features:

- appears frequently into zone I or into a posterior location of zone II;
- no ridge, which appears at to the so called "classical" ROP;
- the contrast between the intensity of plus signs and the "apparent" early stage of ROP;
- the evolution towards advanced stages is fast, without passing successively through all stages.

Threshold disease is defined by the Cryotherapy for Retinopathy of Prematurity Study (CRYO-ROP Study) [1] as at least five continuous or eight cumulative clock hours of stage 3 retinopathy in zone I or II with plus disease. The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity Study (STOP-ROP Study) [2] differentiates between zone I and II regarding to threshold disease. Thus, if for zone II the same criteria are used as for the CRYO-ROP study, for zone I, threshold ROP is considered in any stage of ROP with plus disease or ROP stage 3, no matter if there is plus disease or not. The Early Treatment for Retinopathy of Prematurity Study (ETROP Study) [3] recommends an earlier laser treatment, for the stages considered prethreshold, by giving a greater importance to ROP type I which needs to be treated.

These prethreshold stages include:

- ROP type 1:
  - Zone I ROP – any stage with plus disease;
  - Zone I ROP – stage 3 without plus disease;
  - Zone II ROP – stage 2 or 3 with plus disease;
- ROP type 2:
  - Zone II ROP – stage 1, 2 or 3 without plus disease.

Type 2 of ROP should be detected, and undergo treatment only when the disease progresses to type I or threshold stage.

There are many screening protocols worldwide, each of them being adopted according to the development level and, implicitly, by the level of neonatal care of that country. According to The American Guidelines [4], it is recommended to stop screening in one of the following conditions:

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- the complete vascularization of zone III;
- the postmenstrual age (PMA) of 45 weeks;
- the complete regression of ROP.

After the acute phase of ROP, the infants are monitored at intervals of 3 to 6 months, depending on the presence of ROP and severe forms of disease.

The treatment applied into the prethreshold or threshold stages of disease is laser therapy and/or intravitreal injections with drugs against vascular endothelial growth factor (anti-VEGF). The structural and functional results depend on the so-called "therapeutic window". This therapeutic window, with a time range of 24 to 72 hours depending on disease severity, is the time interval in which the treatment can be applied.

Material and methods

The study population consisted of 503 preterm infants born between January 2008 and January 2012. All these infants, born or transferred to Neonatology Intensive Care Unit or admitted in Tîrgu Mureș Premature Neonatology Clinic, presented risk of developing ROP, and, therefore, they needed rigorous screening for retinopathy of prematurity.

As criteria for inclusion we used:

- premature newborn with GA ≤ 34 weeks and BW ≤ 2000 g;

and as exclusion criteria we used:

- premature newborn with GA > 34 weeks and/or BW > 2000 g;
- preterm infants with congenital anomalies;
- newborn on term.

After a prior dilation of the pupil with tropicamide 0.5% and phenylephrine 2.5%, indirect ophthalmoscopy with scleral indentation was applied on all premature infants. Direct ophthalmoscopy or slitlamp examination, after topical anesthesia and eye speculum insertion were performed in cases where a damage of the anterior ocular segment was suspected.

The study population was divided according to:

1. gestational age:
   - GA ≤ 28 weeks;
   - 28 weeks < GA ≤ 32 weeks;
   - 32 weeks < GA ≤ 34 weeks;
2. birth weight:
   - BW ≤ 800 g;
   - 800 g < BW ≤ 1000 g;
   - 1000 g < BW ≤ 1500 g;
   - 1500 g < BW ≤ 2000 g.

The laser treatment was performed in pretreshold and threshold cases into two university medical centres located in Cluj Napoca and Brașov (between January 2008 and July 2011) and then (starting with August 2011) at Neonatology Intensive Care Unit of Tîrgu Mureș.

Statistical analysis

The clinical data were evaluated using the chi-square test. Differences were considered to be statistically significant for p values smaller than 0.05.

Results

Our study was conducted on a sample of 503 premature infants with GA ≤ 34 weeks and BW ≤ 2000 g, who were followed up until their corrected age (PMA) was at least 45 weeks. This group represents only 94% of all premature infants included in the initial examination (535 premature infants). From the other 6% six babies died before the completion of screening and another 26 babies did not follow up a full process of screening.

From 503 infants, 237 were girls (47.1%) and 266 boys (52.9%). From them, 121 (24.1%) have developed various stages of ROP, while 382 (75.9%) did not have any type of retinopathy of prematurity. Regarding the incidence of ROP, a gradual increase was noticed, from 13.6% in 2008–2009 to 34.8% in 2011–2012 (Table I).

The distribution of eyes by the ROP stages is illustrated in Table II, and by ROP zones in Table III. From those six cases of ROP stage 5, three had APROP.

Statistical analysis of the data showed that GA and BW are risk factors for the development of ROP ($p < 0.0001$), with a decreasing risk as these values were higher. Both data series are presented in Figure 1.

Laser treatment was applied to 20 infants, which means 4.0% of all premature babies, and 16.5% of those with ROP respectively. Eighteen children (90%) received laser treatment on both eyes, while 2 patients (10%) were treated only on one eye. While in 16 cases (80%) a positive development after laser treatment was obtained, in 4 cases (20%) the disease has progressed toward retinal detachment. Of the four cases that have evolved unfavourably, three were APROP and one had a "classical" ROP zone I, suggesting a strong association between severe forms of disease and the failure of laser treatment. All threshold and pretreshold cases have developed a favourable outcome after treatment.

Table I. The incidence of ROP

Period	2008–2009	2009–2010	2010–2011	2011–2012
Infants	110	105	150	138
ROP cases	15 (13.6%)	22 (21.0%)	30 (20.0%)	48 (34.8%)

Table II. Sample distribution regarding the stages of ROP

ROP stage	1	2	3	4	5
Infants	34 (28.1%)	65 (53.7%)	16 (13.2%)	0	6 (5.0%)

Table II. Sample distribution regarding the stages of ROP

ROP zone	I	II	III
Infants	10 (8.3%)	96 (79.3%)	15 (12.4%)

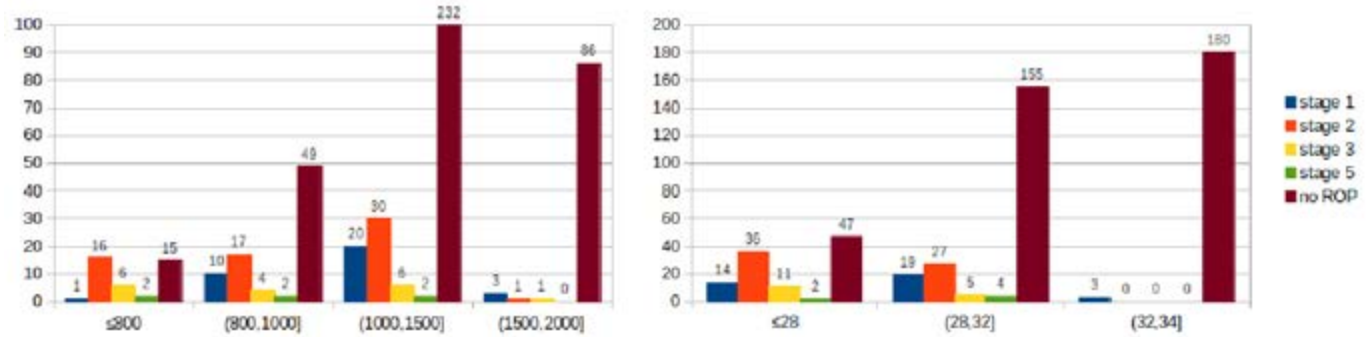

Fig. 1. The distribution of cases by BW and GA values, respectively

For those who required laser therapy, the mean GA was 27.9 weeks with a standard deviation of 2.2 weeks, while the average BW was 949.5 g with a standard deviation of 246.8 g. The postmenstrual age (PMA) when the laser treatment was applied was 36.9 weeks (with a standard deviation of 2.3 weeks).

Regarding the laser treatment according to GA and BW, we obtained an increased frequency of laser treatment for premature group with BW ≤ 800 g (9 cases) and GA ≤ 28 weeks (14 cases), and fewer cases into the group of those with 1000 < BW ≤ 1500 g (5 cases) and 28 < GA ≤ 32 weeks (6 cases). None of the infants within the group of 32 < GA ≤ 34 weeks or 1500 < BW ≤ 2000 g required laser therapy.

Statistical analysis showed that a lower value of BW has an increased importance into the occurrence of disease forms which require laser therapy (p = 0.0058). No statistically significant association was found between GA and cases which needed laser therapy (p = 0.0789).

Some complications appeared due to laser therapy, in six of our cases:

- vitreous haemorrhage – 4 cases;
- hyphema – 1 case;
- corectopia – 1 case.

Discussions

Criteria for screening of preterm vary from country to country, due to different levels of neonatal care. For children with GA below 32 weeks and BW under 1500 g, most countries have adopted criteria proposed by the American Society of Ophthalmology in 2006 [4]. Therefore, most of epidemiological studies are based on these criteria. Almost all medical centres of our country adopted the American criteria, but in Tîrgu Mureș these criteria were extended to GA ≤ 34 weeks and BW ≤ 2000 g, following the suggestion of Bucharest team [5] who has recorded cases of ROP that require treatment for premature infants with a higher limit in GA and BW.

The incidence of 24.1% for ROP which was found in our study is comparable to the incidence of ROP in other countries with high levels of neonatal care [6,7,8,9]. In a previous study conducted in our medical centre between 2008 and 2010, the incidence of ROP was 21.9% for babies with GA less than 32 weeks and BW less than 1500 g [10]. Our values for incidence are similar with those obtained in Cluj Napoca medical centre (26%) [11], but smaller than those noticed in the south part of our country (55%) [5].

We consider that the continuous increase of ROP incidence, from 13.6% in 2008 to 34.8% in 2012, is determined by two factors: getting experience in the peripheral fundus examination resulting in more peripheral ROP detection, and the development of neonatal care by raising the abilities to keep alive prematures with lower gestational age.

ROP zone I incidence (8.3%) is also comparable to that found in the ETROP study (9.1%) [3]. We obtained similar results for the ROP incidence related to gestational age and birth weight, compared to those obtained by some international epidemiological studies [7,12,13,14]. Thus, as was proved before, GA and BW are highly significant risk factors for the development of ROP, with a risk reduction as the values of gestational age and birth weight were higher.

The incidence of ROP for infants group with GA > 32 weeks was 1.63% and for BW > 1500 g an incidence of 5.49% was obtained. These percentages are lower than those obtained into the south part of our country, where Vatavu et al. [5] reported an incidence of 12.6% for GA, respectively 26% for BW. We explain these differences through the fact that some children have been transferred from other centres, with a lower level of neonatal care compared to Bucharest, which is the national centre for screening and treatment of ROP.

There were no cases of stage 4 ROP which required vitreoretinal surgery for two reasons:

- stage 5 was present at first examination;
- stage 4 was an intermediate step to stage 5, after an unfavourable evolution of laser treatment.

3.97% of the examined infants, and 16.81% of children with ROP had required laser therapy. The incidence reported by other studies [6,15,8] is generally greater than ours (within the range 5.2–11.2%), except the study of Mathew et Fern (1.5%) [16]. Comparing our data to another Romanian studies, in Cluj Napoca (Talu et al. [11])

and in the south part of our country [5], we observed a greater incidence of laser treated infants (11% and 15.2%, respectively) in those areas.

In our study we achieved a satisfactory outcome, with 80% of treated babies showing a favourable evolution, rate that is comparable to those reported by Talu et al. (84%) [11] or by Vatavu et al. (86.7%) [5]. The CRYO-ROP [1] and ETROP [3] studies reported unfavourable outcome in 21.8%, respectively in 11% of treated babies. The results of the therapy depend on the type of ROP, being significantly better in classic disease than in aggressive posterior disease (APROP) ($p < 0.05$).

The mean gestational age and the mean birth weight of laser treated patients were 27.95±2.2 weeks, and 949.7±246.8 g respectively, slightly smaller than those obtained by Akçakaya et al. (28.6±2.3 weeks and 1,143.5±337.4 g) [9].

From those four cases with an unfavorable evolution after laser treatment, 75% had aggressive posterior ROP (APROP), the negative evolution being a specific feature of this disease.

The small incidence of ROP cases into the group of infants with $32 < GA \leq 34$ weeks (1.6%) and $1500 < BW \leq 2000$ g (5.5%), along with the absence of disease forms that require laser treatment in these groups, prove that ROP screening may be restricted to prematures with $GA \leq 32$ weeks and $BW \leq 1500$ g.

Laser treatment complications, such as vitreous haemorrhage (the most common complication – bleeding from fibrovascular proliferation), are well known in the literature. Another complication, hyphema, appeared once, bilateral, at a child with an increased plus disease, congestion of iris vessels and pupillary rigidity. In this case, due to pupillary rigidity, the pupillary margin was accidentally hit by laser, followed by temporary mydriasis and inferonasal pupillary shift.

Conclusions

The incidence of retinopathy of prematurity in Tîrgu Mureș is similar to that found in countries with high level of neonatal care. The positive outcome after laser treatment is due to early rigorous screening, as well as to appropriate applied technique. The absence of ROP cases that require laser treatment for infants with $GA > 32$ weeks and $BW > 1500$ g proves that ROP screening can be restricted at babies with $GA \leq 32$ weeks and $BW \leq 1500$ g.

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