

Frequency of Risk Factors in Retinopathy of Prematurity In a Sample of Infants from Mureş County

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Objective: To analyze the risk factors involved in retinopathy of prematurity (ROP) and to report the incidence of ROP in premature infants from Mureş county, Romania.

Material and methods: Our study was based on a prospective study of premature infants with risk for developing ROP, based on international protocols, admitted to the Neonatal Intensive Care Unit from Tîrgu Mureş, between March 2008 and March 2010. In the study were included all the premature babies with gestational age ≤ 32 weeks and birth weight ≤ 1500 g, and those with gestational age > 32 weeks and birth weight > 1500 g, but with unstable perinatal evolution. Ophthalmic examinations were started at 4–6 weeks after birth, and followed until complete resolution of ROP or complete maturation of the retina. We used Chi square test and Fisher test to estimated relative risk (RR), associated with the risk factors of ROP.

Results: In our group of 137 premature babies monitored, 22% were in different stages of ROP. The advanced types of illness that needed therapeutic intervention represented 3% of all premature babies monitored and 13% of all babies with ROP. We found a statistically significant association between low birth weight (≤ 1500 g), low gestational age (≤ 32 weeks), mechanical ventilation for more than 7 days, intrauterine risk factors (maternal preeclampsia), respiratory distress syndrome, and the development of ROP. We also found a statistically significant association between extremely low birth weight (≤ 1000 g) and the development of severe forms of ROP. The other followed risk factors (blood transfusion, anemia or sepsis) were not linked significantly to the risk of ROP development.

Conclusions: Despite progress in neonatal intensive care, ROP persists and can be explained by greater prematurity and early screening. Effective screening procedures performed between the 4th and 6th week of life can improve the prognosis of the disease.

Keywords: retinopathy of prematurity, risk factors, preterm infants, low birth weight infants

Introduction

Retinopathy of prematurity (ROP) is the main cause of visual impairment in premature infants [1]. The increased survival of extremely low birth weight (ELBW) infants in recent years, due to advances in neonatal care, has produced a population of infants with a very high risk of developing ROP. It has been believed for many years that oxygen therapy increases the risk of ROP in preterm infants. However, ROP can occur even with careful control of oxygen therapy [2]. Several factors increase the risk of ROP, especially those associated with short gestation and low birth weight (BW) [3]. Other identified risk factors include sepsis, inside ventricle hemorrhage (IVH), exposure to light [4], blood transfusions [5] and mechanical ventilation [6].

From the first 16 weeks of gestation through birth, retinal blood vessels grow outwards from the optic nerve to reach the peripheral retina. The last 12 weeks of a normal 40-week gestation are crucial in the development of fetal eyes. In premature infants, the normal growth of blood vessels stops. It is theorized that the area without adequate blood supply emits a chemical trigger to stimulate the growth of abnormal vessels. These vessels lead to the formation of a ring of scar tissue attached both to the retina and the vitreous gel that fills the center of the eyes. As the scar contracts, it may pull out the retina, creating a retinal detachment.

High risk premature infants are usually monitored by a retinal specialist or pediatric ophthalmologist during their hospitalization in a neonatal care unit.

Parents of infants with ROP should be informed of the nature and possible consequences of this disorder throughout the infant's hospital stay, beginning at the time of first diagnosis and continuing with updates on its progression during hospitalization.

Guidelines for screening premature infants at risk for ROP adopted in our country are the same used by the American Academy of Pediatrics (2008), mentioning that the screening of all premature infants with low birth weight (BW) ≤ 1500 g and/or gestational age (GA) ≤ 32 weeks or GA > 32 weeks and/or BW > 1500 g with unstable perinatal evolution is required [7]. Depending on severity, ROP is classified in five stages (1–5). Stages 1 and 2 need observation, stage 3 (+) needs retinal laser photocoagulation, while stage 4 and 5 require vitreo-retinal surgery.

The plus sign (+), considered as a sign of aggressiveness of the disease consists of: tortuosity of veins of the posterior pole, dilated iris veins, poor pupil expansion, vitreous haze.

In the last 3 years, we monitored the frequency of ROP in our area and the risk factors involved. Our aim was to identify ROP cases along with the risk factors involved, and to intervene promptly with proper therapy.

Methods

Between March 2008 and March 2010 we examined all premature infants with risk for ROP, admitted to the Neonatologic Intensive Care Clinic from Tîrgu Mureş, Romania.

Eligibility criteria used were:

- ▶ premature newborn: GA ≤ 32 weeks, BW ≤ 1500 g;
- ▶ premature newborn: GA > 32 weeks and BW > 1500 g with unstable perinatal status.

We excluded preterm infants with > 32 weeks, with > 1500 g of weight but with stable evolution, newborns on term and also preterm infants with congenital abnormalities.

Gestational age (GA) was determined by the best obstetric estimate of GA on the base of the last menstrual period (LMP) registered, ultrasound and postnatal physical examination.

ROP was diagnosed based on fundus examination with scleral indentation using indirect ophthalmoscopy and 28D, 40D Volk lenses. Fundus examination was performed after previous pupil expansion and topical anesthesia.

Statistical analysis was performed using a 2×2 contingency table, Chi square test and Fisher test, and a p value of < 0.05 was considered statistically significant.

Results

From our group of 137 premature infants monitored, 63 were girls (45.98%) and 74 boys (54.02%), with a small predominance of boys.

The incidence of ROP in our group was 21.89% of all premature infants examined.

The distribution of the stages of ROP was:

- ▶ stage 1 = 14 cases (46.66% of the group with ROP and 10.21% of all preterm infants monitored);
- ▶ stage 2 = 12 cases (40% of the group with ROP and 8.75% of all preterm infants monitored);
- ▶ stage 3 = 4 cases (13.33% of the group with ROP and 2.91% of all preterm infants monitored);
- ▶ stage 4 = 0 cases (0%);
- ▶ stage 5 = 0 Cases (0%).

The advanced types of illness that needed laser intervention (above stage 3), represented 2.91% of all premature babies monitored and 13.33% of all babies with ROP (Table I).

We identified five main risk factors which were statistically significant for ROP:

- ▶ GA ≤ 32 weeks, (p < 0.0001 , RR=8.833);
- ▶ BW ≤ 1500 g (p < 0.0004 , RR=10.73);
- ▶ mechanical ventilation for more than 7 days (p < 0.0001 , RR=15.33);

Table I. Frequency of laser treatment applied to premature with or without ROP

Samples of infants monitored	With laser treatment applied (%)	Without laser treatment applied (%)
Group of all premature babies (137)	3%	97%
Group of premature babies with ROP (30)	13%	87%

- ▶ intrauterine risk factors associated (maternal preeclampsia) (p < 0.0001 , RR=3.657);
- ▶ respiratory distress syndrome (RDS) (p < 0.0001 , RR=8.203).

Other risk factors like sepsis (p=0.0592, RR=8.133), blood transfusion (p=1, RR=0.8133), anemia (p=0.068, RR=3.63), IVH (p=0.058, RR=2.483), were considered not significant for ROP, in our study (Table II).

Discussion

The incidence of ROP and laser therapy interventions are different from country to country. It is difficult to compare the studies made on this topic because of the differences between inclusion criteria used, the epidemiology of prematurity and resuscitation techniques.

CRYO-ROP (Cryotherapy for Retinopathy of Prematurity) study was the most complex study made on this subject in the USA, based on a group of 4099 newborn babies born with BW < 1500 g and with an incidence of ROP of 65.8% and newborn babies with BW < 1000 g, with 70% of ROP [8].

ETROP (Early Treatment for Retinopathy of Prematurity) study was a multicentric study also focused on ROP incidence. Incidence of any ROP stage reached 68%, and the frequency decreased sharply with the increasing of BW and GA [9].

In our study, the incidence of ROP (21.89%) is comparable to the incidence of ROP in the world (between 16–60%) [10], especially to that of developed countries with a high level of neonatal care [11,12].

Comparing our results with other recent studies [13,14], it is confirmed that the incidence of threshold forms of the disease, which require laser therapy is inversely related to GA and BW, being practically absent in babies with GA > 32 weeks and BW > 1500 g.

Comparing our data (which came from a centered area of our country) to another Romanian studies from southern areas, we observed a lower frequency of ROP (21.89% against 55% [15] and 77% [10]). Also in our study, only 2.91% of the cases needed laser therapy compared to 15.6% in the southern areas [10,15].

Table II. Correlations between risk factors and retinopathy of prematurity in infants from Mureş county

Risk factors	Frequency No (%)	p value	Relative risk (RR)
GA ≤ 32 weeks	84 (61%)	p < 0.0001	8.833
BW ≤ 1500 g	100 (73%)	p < 0.0004	10.730
Mechanical ventilation > 7 days	45 (33%)	p < 0.0001	15.333
Intrauterine risk factors	58 (42%)	p < 0.0001	3.657
RDS	32 (23%)	p < 0.0001	8.203
IVH	29 (21%)	p=0.058	2.483
Sepsis	15 (11%)	p=0.0592	8.133
Blood transfusion	19 (14%)	p=1	0.8133
Anemia	21 (15%)	p=0.058	3.683

Vatavu *et al.* [10] explains that the increased incidence of ROP might be due to the fact that their hospital is the national center for diagnosis and treatment of ROP and the most of high-risk premature infants from the southern areas and from centers without a high level of neonatal care are addressing this hospital.

In recent years, a decreased incidence of ROP was proven, many authors explaining this by progresses achieved in neonatal care.

The Dutch study [16], also shows a decrease in the incidence of ROP from 40.9% to 20.6% in 2005. This improvement could explain the difference between our data and the CRYO-ROP results: ROP incidence of 21.89% in our study compared to 65.8% of CRYO-ROP, in the BW <1000g group: 45% compared to 70% from CRYO-ROP [8].

The incidence of ROP needing laser treatment in our study was less than 3%, which is comparable to other reports, some studies reporting an incidence of less than 5% for severe ROP needing laser treatment [17]. Shah *et al.* [18] reported zero incidence of severe ROP needing treatment and attributed it to a protocol of improved management of oxygen administration. In our study, we did not identify any patients in stage 4 or 5, possibly because of the early screening, early diagnosis and early therapy of ROP.

The main risk factors for developing ROP, proved by our study too, are low GA and BW. The lower the birth weight and gestational age are, the more severe postnatal hypoxia is and oxygen is used more frequently, resulting in a higher incidence of ROP.

Days of mechanical ventilation (more than 7) were identified as independent predictors of the occurrence of ROP. This finding fits with the observation that in general, neonates who develop ROP are born at early gestational age, also have low birth weight, and are medically unstable, requiring maximum intervention.

In addition, this study reveals an intrauterine risk factor (maternal pre-eclampsia), which is associated with chronic intrauterine stress, as a statistically independent factor and as having an influence on the incidence of ROP [19].

Respiratory failure secondary to surfactant deficiency is a major cause of morbidity and mortality in low birth weight immature infants. Surfactant therapy substantially reduces mortality and respiratory morbidity for this population. Respiratory insufficiency may be a component of dysfunction in multiple organs in sick infants, also an important factor in the pathogenesis of ROP.

Other factors, such as anemia, blood transfusion, infection, and HIV, did not show a significant correlation with ROP in our study, compared to other studies.

Conclusion

The incidence of ROP and of threshold forms of the disease in Mureş county is comparable to that in developed countries, but it is much lower than in the south of the country, this fact being due mainly to the high level of neonatal care.

It is important to know all the risk factors involved in this particular disease, in order to be able to diagnose it early and to implement an efficient intervention to reduce its frequency and the complications involved.

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