

Research Article

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Correlation of retinopathy of prematurity with bronchopulmonary dysplasia

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Abstract: Retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) are diseases that occur only in preterm infants. The etiology of these disorders is multifactorial; however, it is believed that some of the factors in children presenting with BPD affect both the initiation and severity of ROP. The aim of the study was to evaluate the degree of clinical severity of ROP in infants with BPD compared to those without BPD.

Methodology: Infants were divided into two groups: the BPD+ study group and BPD- control group. Parameters including the incidence of ROP and its severity were compared.

Results: In neonates with BPD, more severe forms of ROP occurred significantly more frequently than in infants without BPD. Newborns with BPD required significantly longer use of mechanical ventilation; moreover, the number of days in which the concentration of oxygen in the respiratory mixture exceeded 50% was greater in BPD+ children. Children with BPD also received more blood transfusions compared to children without BPD.

Conclusions: Newborns in the BPD+ study group showed advanced stages of ROP more often than newborns in the BPD- control group. The etiology of ROP and BPD is multifactorial; however, our findings suggest oxygen plays a significant role in the development of these diseases.

1 Introduction

Retinopathy of prematurity (ROP), an ocular disease characterized by an arrest of normal retinal neuronal and vascular development, is a major cause of visual impairment and blindness in preterm infants [1].

Risk factors for the development of ROP are reported to include: hyperoxia and long-term oxygen therapy, artificial ventilation (especially that which lasts longer than 7 days), periods of hypoxemia after completion of oxygen therapy, bronchopulmonary dysplasia (BPD), respiratory failure, numerous blood transfusions, anemia, sepsis, necrotizing enterocolitis, metabolic acidosis, low Apgar scores, asphyxia, intraventricular hemorrhage, numerous apneas, congenital heart disease, abnormal glucose, hypotension, pneumothorax, prenatal and postnatal steroid therapy, use of antibiotics and xanthine compounds such as aminophylline and theophylline, treatment of patent ductus arteriosus with indomethacin, phototherapy for jaundice, poor nutrition, and parenteral nutrition [1-4]. In addition, repeated blood transfusions are reported to be a potential risk factor for ROP [5,6]. Fetal hemoglobin (HbF) can more easily bind oxygen than it can release it to tissues. The percentage of HbF in preterm infants is generally reported to be >80% [7]; however, this percentage increases with the newborn's immaturity. This mechanism is, in part, the body's physiological protective response to an excess of oxygen. As blood containing hemoglobin A is used for transfusions, HbF is replaced by adult-type hemoglobin (HbA), the properties of which are inverse to HbF; i.e., it can more easily release oxygen to tissues than it can bind to the oxygen. This can lead to the development of hyperoxia in the retina and the formation of oxygen-free radicals, which increases the risk of the development of ROP [1,4,8,9].

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In the course of sepsis, the inflammatory response results in increased production of inflammatory mediators, including interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α), and thromboxane (TXA), all of which damage the vascular endothelium, and consequently contribute to hypoxia of the retina. Retinal hypoxia induces the release of vascular endothelial growth factor (VEGF), which is responsible for neovascularization in the retina [1,3,8]. Furthermore, there is excessive activation of macrophages and the level of oxygen free radicals increases [8,9]. Csak *et al.* emphasize the role of genetic factors that may predispose a person to the development of ROP [10]. The polymorphism of the gene encoding VEGF is important here. Perhaps in the future, it will be possible to accurately predict the risk of development and progression of retinopathy by evaluating the polymorphism of VEGF [10-12]. This possibility is supported by previous findings of similarity between the mutation in the gene responsible for the development of ROP and in the gene for Norrie syndrome, an X-linked genetic disorder with a congenital exudative vitreoretinopathy. It may be manifested by microphthalmia and blindness due to early inhibition of the peripheral vasculature of the retina [13]. This similarity indicates that genetic predisposition may underlie ROP.

Alternatively, Poggi *et al.* [14] claim that haplotypes of VEGFA and endothelial nitric oxide synthase (eNOS) may be independent protective factors or risk markers for prematurity complications. Also, Kusuda *et al.* [15] showed that multivariate analyses indicated that low birth weight, blood transfusion and respiratory distress syndrome, but not genetic polymorphism in VEGF, were risk factors for advanced ROP.

Many other factors are key to the development of the brain and eye in the fetus, and thus to the potential development of retinopathy. A deficiency of essential unsaturated fatty acids, for example, may contribute to the development of ROP [1,8]. Furthermore, given vitamin E (alpha-tocopherol) is a natural antioxidant and protects the retina from effects of oxygen free radicals, a deficiency of this vitamin may be a risk factor for development of retinopathy. In preterm infants born before 28 weeks of gestational age, a complete lack of alpha-tocopherol, and the protein responsible for the transport of vitamin E into the nerve cells of the retina, is observed. Therefore, in these preterm babies, even the small amount of oxygen needed for normal activity of the nervous system may contribute to the occurrence of ROP [16].

BPD was first described by the radiologist William Northway in 1967 [17], and this definition was redefined in 2001 by Jobe and Bancalari [18]. This new classification of

BPD includes newborns born before 32 weeks' gestation and includes oxygen dependency at the 28th day of life and the 36th week of postconceptional age (or the age at which the infant is permitted to leave the hospital, if earlier).

In the pathogenesis of BPD, growth factors such as VEGF, IGF-1 and transforming growth factor β (TGF β) are also important. These factors regulate the process of lung morphogenesis and thus impact the pre- and post-natal development of the lungs. Disorders in the secretion of VEGF, IGF-1, and TGF beta cause a series of changes typical of BPD. VEGF is responsible for regulating angiogenesis, formation, differentiation, maturation and repair processes of the vessels. Excessive TGF- β inhibits morphogenesis and increases pulmonary fibrosis, contributing to the development of BPD. IGF-1 regulates the maturation and repair processes of the lungs. It has been shown that in children with BPD, IGF-1 concentration is lower than in children without BPD at the same postconceptional age. Low concentrations of this factor disrupt normal angiogenesis and reduce the synthesis of VEGF. It has been shown that both the presence of low serum IGF-1 levels after preterm birth and the interaction between IGF-1 and VEGF are important in the development of both BPD and ROP [12].

Similar to the retinopathy of prematurity, postnatal inflammation has an impact on the development of BPD [19].

Oxygen therapy plays an important role in the pathogenesis of BPD. Preterm neonates are known to require oxygen therapy to prevent respiratory failure due to immaturity of the lungs. This is often long-term oxygen therapy with high concentrations of oxygen in the respiratory mixture. Hyperoxia impairs lung development, inhibiting alveolarization and angiogenesis. As a result, the surface of gas exchange is reduced. In the case of surfactant deficiency and infection, the lungs of neonates are even more susceptible to the damaging effects of oxygen and artificial ventilation [20-22].

2 Methods

The aim of the study was to evaluate the prevalence of ROP and its severity in a population of preterm infants diagnosed with BPD compared to those without BPD, and to analyze the risk factors common to both disease entities. The material for this study constituted the medical records of 97 preterm newborns who were born in the Department of Neonatal Diseases, Pomeranian Medical University in Szczecin, Poland, between 2006 and 2012.

Informed consent was obtained from all parents in an oral form.

The research complied with all the relevant national regulations and institutional policies, was in accordance with the tenets of the Helsinki Declaration, and was approved by the authors’ institutional review board.

The collected documentation related to infants born between 25 and 30 weeks’ gestation, with a birth weight of between 530 g and 1720 g. The analyzed population of preterm infants was divided into two groups depending on the presence or absence of BPD: group 1 included 54 preterm neonates diagnosed with BPD (study group) and group 2 was composed of 43 preterm infants without BPD (control group). To standardize gestational age and birth weight of groups 1 and 2, 23 infants from group 1 and 12 infants from group 2 were excluded. After reducing the size of the two groups, new subgroups were created, and named 1R and 2R, respectively (in order to differentiate from the original groups). Group 1R comprised 31 preterm neonates diagnosed with BPD (study group), and group 2R of 31 preterm neonates not diagnosed with BPD (control group).

In all groups, the occurrence and the severity of ROP in both eyes were retrospectively investigated. The first ophthalmologic examination was performed at 4 weeks of age, and the subsequent examinations were set by an eye care practitioner according to the development of changes in the retina. Depending on the occurrence and stage of ROP, all newborns were classified into groups 1 and 2 ROP: group 1 ROP – no, stage 1 or 2, group 2 ROP – stage 3, 4 or 5 [23].

On the basis of the medical records of the population of newborns, data on occurrence of risk factors for the development of BPD and ROP were collected, and attempts to identify those which simultaneously affected the occurrence and severity of these two diseases were made. Factors analyzed included gestational age (weeks), birth weight (g), sex, respiratory failure, respiratory distress syndrome (RDS), systemic and intrauterine infections, pneumonia, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemor-

rhage (IVH), and anemia. The number of days in which mechanical ventilation was required, and the number of days in which the oxygen concentration in the breathing mixture exceeded 50% was also assessed. In addition, the number of blood transfusions required was also recorded.

2.1 Statistical analysis

Statistical analysis was performed with use of StatSoft, Inc. (2011) STATISTICA (data analysis software system), version 10 (www.statsoft.com). To verify the normal distribution of the quantitative variables (gestational age, birth weight, number of days of mechanical ventilation, number of days in which the concentration of oxygen in the respiratory mixture exceeded 50% and the number of blood transfusions), the Shapiro–Wilk test was used, with the significance threshold level $\alpha = 0.05$. A parametric Student t-test was used in comparisons of variables with normal distribution. Variables with a distribution other than normal were analyzed using a nonparametric Mann–Whitney U test. In the case of qualitative variables, statistical difference was tested with a Chi-square test, V-square test or Chi-square test with Yates’ correction, depending on the expected sample size. The difference was considered statistically significant if $p < 0.05$. Data are presented as median [Me] and (range) or mean [M] ± standard deviation [SD], depending on the normality of the distribution of quantitative variables.

3 Results

In the entire study group, infants with BPD (n = 54) differed significantly in the severity of ROP compared to infants without BPD (n = 43) $p < 0.001$.

In the reduced population of newborns (n = 62), both BPD+ and BPD- groups were homogeneous in terms of gestational age (group 1R BPD+ Me (range): 28 (26–30) weeks; group 2R BPD- Me (range): 28 (26–29) and birth

Table 1: Correlation of the incidence and severity of ROP in neonates with BPD+ (study group) and BPD- (control group) in the population of newborns.

	BPD+ group (n = 31) n (%)	BPD- group (n = 31) n (%)	p	Statistical test
ROP group 1R	22 (70.97%)	30 (96.77%)	0.006	Chi-square test with Yates’ correction
ROP group 2R	9 (29.03%)	1 (3.23%)		

weight (group 1R BPD+ $M \pm SD$: 1048 ± 204 g; group 2R BPD- $M \pm SD$: 1138 ± 201 g). There was no statistical difference in the sex of the newborns included in the BPD+ and BPD- groups (group 1R vs 2R: $p = 0.123$).

The results of the analysis showed that children with BPD differed significantly in the severity of ROP compared to children without BPD (1R vs 2R: $p = 0.006$). This was confirmed by the fact that BPD is one of the factors affecting the development of ROP, or at least, BPD accompanies ROP in preterm neonates. Selected clinical characteris-

tics of newborns in the study population are presented in Table 2.

The two groups differed significantly in the occurrence of respiratory distress syndrome ($p < 0.001$). In children with BPD, mechanical ventilation time was significantly longer ($p < 0.001$; Me (range): 30.0 (2–81) days) compared to children without BPD (Me (range): 3 (0–33) days). Similarly, in the group of infants with BPD, there were significantly more days in which the concentration of oxygen in the respiratory mixture exceeded 50% compared to those infants without BPD ($p < 0.001$). Newborn babies from the

Table 2: Summary of clinical data of newborns with BPD+ (study group) and BPD- (control group).

	1R group (BPD+) n = 31		2R group (BPD-) n = 31		p	Statistical test
	n	%	n	%		
Gestational age Me (range)	28 (26-30)		28 (26-29)		0,38	Mann–Whitney U
Birthweight $M \pm SD$	1048 \pm 204		1138 \pm 201		0,086	T-Student
Sex	male n (%)	16 51,61%	10 32,26%		0,1225	Chi-square
	female n (%)	15 48,39%	21 67,74%			
Respiratory failure (SIMV, nCPAP)	31	100.00%	21	62.79%	0.002	Chi-square with Yates' correction
Respiratory distress syndrome (RDS)	31	100.00%	19	61.29%	< 0.001	V-square
Number of days of mechanical ventilation; Me (range)	30	(2–81)	3	(0–33)	< 0.001	Mann–Whitney U
Number of days with FiO_2 exceeding 50%; Me (range)	7	(0–70)	0	(0–12)	< 0.001	Mann–Whitney U
Sepsis	9	29.03%	12	38.71%	0.421	Chi-square
Intrauterine infection	16	51.61%	5	16.13%	0.003	Chi-square
Pneumonia	19	61.29%	9	29.03%	0.012	Chi-square
Patent ductus arteriosus (PDA)	8	25.81%	6	19.35%	0.547	V-square
Intraventricular hemorrhage (IVH)	17	54.84%	10	32.26%	0.073	Chi-square
Necrotizing enterocolitis (NEC)	9	29.03%	4	12.90%	0.119	V-square
Anemia	31	100.00%	30	96.77%	1.00	Chi-square with Yates' correction
Number of blood transfusions (PRBC); Me (range)	5.68	(1–13)	3.16	(0–8)	< 0.001	Mann–Whitney U

BPD+ group also had significantly more blood transfusions than newborns without BPD ($p < 0.001$; group 1, Me (range): 5.68 (1–13); group 2, Me (range) 3.16 (0–8)).

4 Discussion

The correlation of the incidence and severity of ROP with the presence of BPD was observed in the analyzed population of newborns. The results of analysis showed the relationship of these two disease entities. In a previous study, Guven et al. and Kornacka et al. also showed a correlation between the occurrence of higher severity ROP and the presence of BPD [21,24]. BPD occurred more frequently in children with stage 3 or 4 ROP (10/11 newborns) compared to those without ROP (1/11 newborns) and those with stage 1 or 2 ROP (4/8 neonates). Holmström et al. concluded that BPD, as it precedes ROP and is a risk factor for ROP, increases the severity of ROP and may also be a predictive factor for the development of that disease [25]. According to Higgins et al., ROP develops more frequently in newborns with comorbid BPD [26]. Research by Guven et al. and Leviton et al. also provides support for a relationship between the diseases [21,27]. According to these authors, the presence of BPD in infants requires oxygen therapy, which can then result in a higher incidence of ROP due to immature antioxidant systems. A study by Krzysztofowicz et al. also confirmed the correlation between advanced stages of ROP and BPD, with 71% of preterm infants with the most severe forms of ROP confirmed to have BPD [28]. These authors stated that the cause of the simultaneous occurrence of both diseases could be explained by the oxygen and steroid therapy.

In our study, the most severe stages of ROP occurred in those children with BPD. These observations are consistent with the findings of Shah et al. [29] and Allegaert et al. [30], who have stated that long-term mechanical ventilation and/or nasal continuous positive airway pressure (nCPAP) assisted ventilation is a causative factor in the development of severe forms of ROP. According to Yang et al. [31] and Seiberth et al. [32], mechanical ventilation increases the severity of ROP. In addition, many researchers have stated they believe free radicals generated as a result of oxygen excess impact the development of ROP and BPD [8,9,33]. In cases of ROP and BPD, free oxygen radicals are formed as a result of increased partial oxygen pressure, which is related to the amount of oxygen delivered during oxygen therapy and mechanical ventilation.

The relationship between ROP and BPD appears to be complex and modified by various factors. In a large inter-

national randomized controlled trial the effects of targeting an oxygen saturation from 85% to 89% compared with a range of 91% to 95% were evaluated. The infants in the lower-target group for oxygen saturation had a reduced rate of ROP ($p=0.045$) and no significant difference in BPD. It should be stressed that targeting an oxygen saturation below 90% in extremely preterm infants was associated with an increased risk of death [34].

Surprisingly, such factors as diet may be important in the development of ROP and BPD. Infants having an exclusive human milk-based diet (HUM) and those receiving a bovine-based diet (BOV) in a large research group (1587 infants with a birth weight < 1250 g) were compared. The HUM group had a significantly lower incidence of mortality, necrotizing enterocolitis, late-onset sepsis, BPD ($p = 0.0015$), and ROP ($p = 0.003$) [35].

Some help in understanding the relationship between BPD and ROP is provided by animal models of both diseases. Based on the research on rat pups, the authors proved that hyperoxia exposure impaired lung, brain and retina structures. Moreover, more severe lung injuries correlated with more severe brain and retina injuries [36].

Many researchers also claim that numerous blood transfusions increase the risk of the development of ROP and BPD [5,6,15,37].

A significantly higher incidence of intrauterine infection in the group of children with BPD compared to those without BPD was observed in our population of preterm neonates. Intrauterine and postnatal infection is a risk factor for the development of BPD [8,19,27,38] and can influence the development of BPD and ROP. These findings were confirmed by observations of preterm infants who had an infection of the fetal membranes in their fetal life and serious complications, such as BPD and ROP, in the neonatal period. On the other hand, there are scientific reports which question the validity of the previously reported relationship, arguing that there is no correlation between chorioamnionitis (CA) and BPD. This inconsistency may be due to differences in populations, definitions, methods and other factors, such as gestational age or use of the antenatal steroids [39,40]. Triple I, a new concept for chorioamnionitis, may prove to be helpful in future data analysis including the relationship between CA and BPD [41].

The role of genetic factors that may confer a predisposition to the development of ROP and/or BPD is equivocal.

In conclusion, newborn babies with BPD required significantly more aggressive oxygen therapy, and they more often showed advanced stages of ROP than newborns without BPD. The etiology of ROP and BPD is multifacto-

rial. It can be supposed that oxygen plays a significant role in the development of the two diseases.

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