PRACE KAZUISTYCZNE
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Iris rubeosis, severe respiratory failure and retinopathy of prematurity – case report

Rubeoza tęczówki, ciężka niewydolność oddechowa i retinopatia wcześniaków – opis przypadku

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Abstract

The aim: *Case study reports for the first time about development of massive iris neovascular complication in course of retinopathy of prematurity related to systemic and ocular ischemic syndrome due to tracheostomy-requiring extremely severe premature respiratory failure.*

Material and method: *Premature female, 950 grams birth weight, born from 17-year-old gravida 1, at 28 weeks' gestation by cesarean section due to premature placental abruption with threatening hemorrhages, with 1 to 5 Apgar score. The baby developed severe respiratory failure which required tracheostomy, advanced bronchopulmonary dysplasia treated with steroids (BPD) and respiratory distress syndrome (RDS) with failure to extubate together with secondary ocular ischemia. All the mentioned with multifactorial organs complications (NEC, leucopenia, anemia, pneumonia, periventricular leucomalacia, electrolyte abnormalities and metabolic acidosis) resulted in massive peripupillary iris neovascularization (NVI) in both eyes coexisting with retinopathy of prematurity (ROP) in 38 weeks' PMA infant.*

Ultrasonography-B, slit-lamp and indirect fundus examinations with photography were used to document focusing ocular diagnosis. The previous retinopathy of prematurity screening examinations performed at standard intervals of time starting from four weeks of life, that is 32 weeks' PMA continuing every two weeks did not present typical lesions seen in retinopathy, however in the second zone of retina slightly marked "plus sign" was visible. Ophthalmological examination at 38 weeks' PMA disclosed massive, round capillary dilatation of the minor arterial circle, spreading to the iris periphery form pupillary margin, and narrow pupils which did not fully react to mydriasis. The intraocular pressure was normal. Ultrasound examination revealed major thickening and echo increase of peripheral retina with its partial detachment.

Result: *Diode-laser pan-retinal photocoagulation and cryoapplication was performed leading to successful regression of neovascular anterior segment (rubeosis was no longer visible by slit-lamp examination) as well as inhibition of retinopathy of prematurity progression.*

Conclusion: *In described preterm infant, vasoactive molecules released by the ischemic retina may have induced vasodilation of iridal vessels, therefore increasing the perfusion of segments of the minor arterial circle, rendering them clinically visible by examination. It has been observed that hypoxia besides other inflammatory risk factors may have significant influence not only on the development of severe anterior-neovascular complications but also on rapid progression of advanced ROP stages with omission of typical clinical stages of ROP.*

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Simultaneously retinal laser-panphotocoagulation with cryotheraphy seems to be the beneficial method for treatment of these complications. The therapy is effective and destroys the cells that produce Vascular Endothelial Growth Factor (VEGF) which is known to be the most important key factor in the progression of ROP.

Key words: **rubeosis iridis** / **retinopathy of prematurity** / **ocular ischemic syndrome** / **diode-laser treatment** / **respiratory failure** / **premature multiorgan complications** /

Streszczenie

Cel pracy: *Pierwsze doniesienie, na podstawie opisu przypadku, o rozwoju masywnej rubeozy tęczówki w przebiegu retinopatii wcześniaków, powikłanej układowym i ocznym zespołem niedokrwienia wymagającym tracheostomii z powodu skrajnie ciężkiej niewydolności oddechowej u wcześniaka.*

Materiał i Metody: *Wcześniak, płci żeńskiej, urodzony z masą ciała 950 gram, w 28-ym tygodniu życia płodowego przez cięcie cesarskie z powodu przedwczesnego oddzielenia łożyska z zagrażającym krwawieniem, od 17-letniej ciężarnej, ze skalą Agar od 1-5.*

U dziecka rozwinęła się ciężka niewydolność spowodowana zespołem zaburzeń oddychania (ZZO) z zaawansowaną dysplazją oskrzelowo-płucną wymagająca tracheostomii i włączenia steroidoterapii. Zaburzeniom tym towarzyszyły objawy wtórnego niedokrwienia gałki ocznej. Wszystkie wymienione powikłania wraz z wielonarządowymi takimi jak (martwicze zapalenie jelit, leukopenia, anemia, zapalenie płuc, leukomalacje okołokomorowe, nieprawidłowości elektrolitowe i kwasica metaboliczna) skutkowały masywną okołoźreniczną neowaskularyzacją w obu oczach (NVI) z towarzyszącą retinopatią wcześniaczą (ROP) w 38 tygodniu PMA.

W badaniach: ultrasonograficznym B, w lampie szczelinowej, w badaniu pośrednim dna oka oraz w wykonanej fotografii dna oka udokumentowano rozpoznanie okulistyczne. Poprzednie badania przesiewowe w kierunku retinopatii wcześniaczej przeprowadzone w standardowych odstępach czasu – co 2 tygodnie, rozpoczynając od czwartego tygodnia życia, czyli 32 tygodniu PMA, nie wykazały wówczas typowych zmian obserwowanych w retinopatii, natomiast ujawniły słabo zaznaczony objaw plus w drugiej strefie siatkówki. Ciśnienie wewnątrzgałkowe było w granicach normy. W dalszym przebiegu choroby, badanie USG wykazało znaczące pogrubienie oraz hiperechogeniczność obwodowej siatkówki z częściowym jej odwarstwieniem.

Wyniki: *W leczeniu zastosowano panfotokoagulację siatkówki laserem-diodowym wraz z jednoczasową krioaplikacją poprzeztwardówkową, uzyskując wycofanie neowaskularyzacji (rubeoza tęczówki niewidoczna w badaniu lampą szczelinową).*

Wnioski: *W przypadku opisywanego wcześniaka, wazoaktywne cząsteczki uwolnione przez niedokrwioną siatkówkę mogły wywołać poszerzenie naczyń tęczówki, tym samym, zwiększyć przepływ w kole tętniczym mniejszym co uwidoczniono w badaniu. Zaobserwowano, że niedotlenienie, obok innych zapalnych czynników ryzyka może mieć istotny wpływ nie tylko na rozwój ciężkiej neowaskularyzacji przedniego odcinka oka, ale również na szybką progresję zaawansowanych stadiów ROP z pominięciem typowych dla przebiegu klinicznego stopni tego schorzenia. Panfotokoagulacja siatkówki wydaje się być korzystną metodą leczenia obserwowanych powikłań. Terapia jest skuteczna i niszczy komórki produkujące czynnik wzrostu śródbłonka naczyniowego (VEGF), który uważany jest za kluczowy w rozwoju ROP.*

Słowa kluczowe: **rubeoza tęczówki** / **retinopatia wcześniaków** / **oczny zespól niedokrwienny** / **leczenie laserem diodowym** / **niewydolność oddechowa** / / **powikłania wielonarządowe u wcześniaków** /

Introduction

Advances in antenatal and neonatal care have resulted in increased diagnosis of ocular disorders, including retinopathy of prematurity (ROP). More recently, a wide spectrum of ophthalmic findings in infants of very low birth weight have been reported, from minimal which do not impact visual acuity through strabismus to severe lesions in the form of bilateral retinal detachment that results in blindness. In addition, it has been described that extreme immaturity and coexisting numerous multi-organs complications with respiratory failure definitely worsen the prognosis of final visual organ condition [1, 2]. Neonates with respiratory failure, severe bronchopulmonary dysplasia (BPD) and respiratory distress syndrome (RDS) were seen more frequently with failure to extubate leading to systemic ischemia [3, 4]. It has been previously reported, that steroid application in BPD treatment decreases the incidence of posterior eye segment complications including severe ROP [5-7].

As far as we know, there have been no previous reports of anterior segment ischemia in the form of iris rubeosis associated with hypoxic factor probably as the main cause for anterior segment neovascularisation development and progression of clinical changes in ROP.

This case study reports for the first time the presence of massive rubeosis iridis with rapid progression of ROP and omission of its early stages which was related to systemic and ocular ischemic syndrome combined with extremely severe respiratory

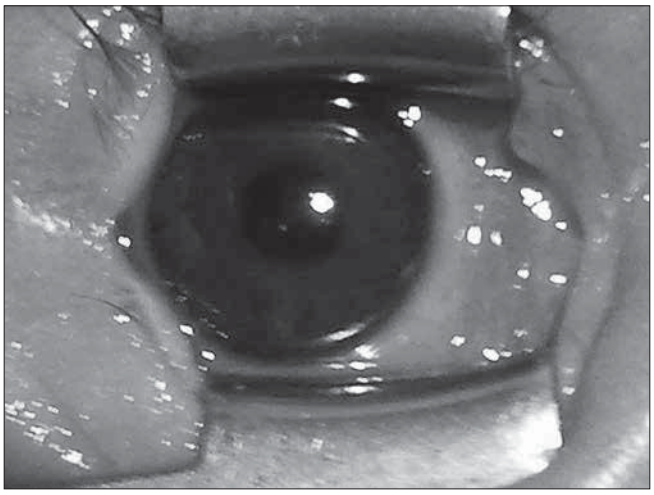

Figure 1. Neovascularization of the iris circle in 38 weeks' PMA infant.

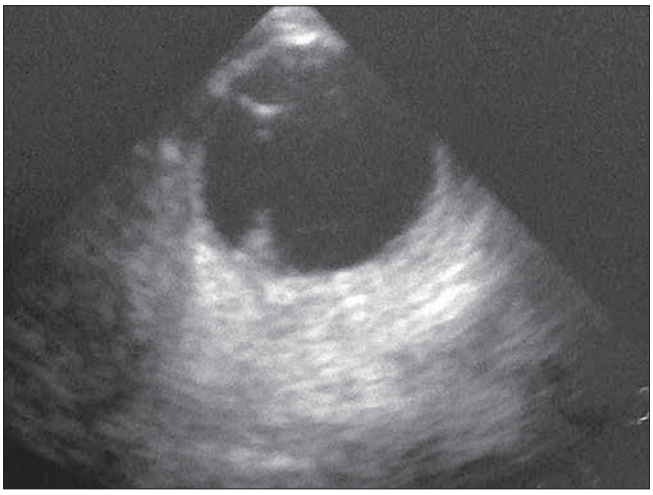

Figure 2. Hyperechogenic extraretinal mass with thickened choroid and vitreous body clouding.

failure although BPD was treated with steroids. Moreover, it provides current concepts on beneficial therapeutic approaches such as simultaneous diode-laser therapy combined with trans-scleral cryoapplication.

Case study

A premature female, 950 grams birth weight, born from a 17-year-old gravida 1, at 28 weeks' gestation by cesarean section due to threatening hemorrhages and severe uterine contractions, with 1 to 5 Apgar score. The infant developed neonatal respiratory distress and high oxygen demand immediately after birth and was admitted to neonatal intensive care unit on nCPAP. Due to persisting respiratory distress, intubation and ventilation were performed. The administered corticosteroid was dexamethasone and treatment regimen was 0.25 mg/kg/day intravenously for 7 days at 34 weeks' postmenstrual age (PMA). Furthermore, over the first few weeks of life, *Enterobacter* and *Stenotrophomonas* colonized fetal lungs. Radiologically confirmed pneumonia and bronchopulmonary dysplasia, with subsequent respiratory distress syndrome (RDS) were the cause for extubating failure, the need for tracheostomy and prolonged mechanical ventilation performed until baby's death in 5 month of life. Necrotizing enterocolitis (NEC) with subsequent post-operative intestine paresis was surgically managed at 30 weeks' PMA. Excision of grossly necrotic segments and exteriorization of viable ends to allow for continued bowel decompression was performed. Colonization of the intestine with *Enterobacter* and *Stenotrophomonas* species was noted at 32 weeks' PMA. Leucopenia, anemia, electrolyte abnormalities and metabolic acidosis were observed in laboratory tests. Numerous packed cell infusions (6 times) were given for anemia (RBC 3,48; HGB 10,5 HCT 31,9). Ultrasound examination of the brain revealed periventricular leucomalacia (PVL).

The previous retinopathy of prematurity screening examination performed at standard intervals of time starting from four weeks of life, that is 32 PMA continuing every two weeks did not present typical lesions seen in retinopathy, however in the second zone of retina slightly marked "plus sign" was visible. Not until 38 weeks' PMA did examination show clinically significant peripupillary neovascularization of the iris (NVI) in both eyes. (Figure 1).

Hand slit-lamp examination disclosed massive, round capillary dilatation of the minor arterial circle, spreading to the iris periphery form pupillary margin. Narrow pupils did not fully react to mydriasis (1% Sol. Tropicamide and 2,5% Sol. Neosynephrine) due to posterior synechia and extended rubeosis iridis, therefore details of the peripheral part of fundus were not possible to assess. Simultaneously, ultrasonography B (ultrasonography – 3300 Echo-Scan ultrasonic B-scan with 10-MHz sector probe equipment-Nidek Co. Japan) confirmed major thickening and echo increase of peripheral retina with partial detachment in both eyes, which might clinically correspond to stage 4 ROP. (Figure 2).

Confluent panretinal diode-laser photocoagulation and preventive peripheral cryotherapy applications in general anesthesia were performed on the second day after the final diagnosis. The follow-up ophthalmic examination on the 7 day revealed dramatic regression of the previously visible rubeotic vessels and confirmation of partial retinal detachment in indirect fundus evaluation and by USG-B. The intraocular pressure was normal (I-care PRO Tonometer (Icare Finland Oy).

Discussion

Ocular neovascularization is a dynamic process which requires a persisting stimulus with hypoxic factors or else the new vessels tend to regress. This destructive secondary angiogenesis is driven by multiple stimuli, among them: inflammation and its products, a hypoxic retina diffusible factor, the "tumor angiogenic factor," vascular endothelial growth factor (VEGF) [8-11] and possibly an aging factor. Accordingly, excessive hyperpermeability and endothelial proliferation are thought to be key steps in neovascularization development of both posterior and anterior eye segment not only in adults but also in prematurity. Iris neovascularization not only in adults, but also in children may occur as a complication of retinal ischemia typically from retinal detachment [12], proliferative diabetic retinopathy [13, 14], vitreoretinopathy [15-17], vein occlusion [18], after surgical management [19, 20] and other reasons such

as exfoliation glaucoma and carotid artery disease [21]. The same as in the newborns, pathological iris vascularization probably might have been due to ischemia in the posterior segment of the eye [22, 23]. It is noteworthy that, it almost never occurs in early neonatal period.

In the presented case, the development of retinopathy in the low-birth-weight premature remained atypical. The proof for this was lack of significant "plus sign" lesions in the posterior pole of the eye as well as the absence of the following stages of clinical course of ROP during the first ophthalmologic examinations, probably because of a very narrow pupil and posterior synechiae. This observation may suggest that apart from different and numerous inflammatory and non-inflammatory risk factors, hypoxia induced by advanced respiratory failure combined with tracheostomy might be very important factor of sudden eye decompensation and diagnosis of 4 ROP. It is likely that higher oxygen levels rescuing the life of premature might have contributed to anterior-neovascularization and formation of vaso-proliferative phase of ROP resulting in partial retinal detachment in the final phase [24-28]. The abovementioned insights are justifiable by the available literature as retinal detachment is a well -recognized cause of rubeosis iridis and is a sufficient stimulus for the development of iris neovascularization in experimental models [22, 29]. It is possible that minor and major iris circle circulation insufficiency in long posterior and anterior ciliary arteries (LPCA, ACA) might stimulate the epithelial cells of the ciliary body or other anterior eye-segment tissues to produce VEGF protein [30]. Importantly, correlation between VEGF and neovascularization in anterior segment of the eye was confirmed by Shah et al. by beneficial antiangiogenic drug application [31]. Diode laser treatment and cryotherapy in this case has shown to cause a successful regression of neovascular anterior segment complications [32], VEGF and fibroblastic activity suppression as well as inhibition of retinopathy of prematurity progression [8, 33].

Conclusion

In summary, understanding both the neonatal causes influencing the development of eye-ischemia emphasizing the role of hypoxic factors and the pathophysiological processes leading to iris rubeosis is crucial to prevent the sight-threating neovascularization in the premature infant. Panretinal photocoagulation seems to be the only effective method of treatment for premature rubeosis iridis, in course of retinopathy of prematurity coexisting with severe respiratory failure.

Oświadczenie autorów

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