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Retinopathy of Prematurity - a literature review

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Abstract:**Introduction and purpose**

Retinopathy of prematurity (ROP) is a rare ophthalmological disease affecting prematurely born infants. The aim of this review is to provide a comprehensive review of ROP, with a focus on its pathogenesis, epidemiology, classification and treatment.

State of knowledge

Retinopathy of prematurity has been recognized for over 80 years. Since then, a standardized classification system: the International Classification of Retinopathy of Prematurity (ICROP) has been developed, with the most recent (third) revision published in 2005. Treatment options have evolved from cryotherapy to laser photocoagulation and intravitreal anti-VEGF injections. Surgical options, such as scleral buckling and vitrectomy are reserved for severe cases of ROP. Although the majority of ROP cases are mild and self-limiting, severe ones can lead to serious ophthalmic and non-ophthalmic consequences. Early detection and treatment are therefore of critical importance.

Conclusions

Retinopathy of prematurity remains a significant global health concern. Effective prevention relies on careful administration of supplemental oxygen, with targets oxygen saturation levels between 90 and 94%, balancing the risks of ROP and mortality. That remains a challenge, primarily in middle- and low income countries. While various agents have been tested as explored as potential prophylactic therapies, further research is needed in this area.

Therapeutic approaches have improved over time and are generally effective. Intravitreal anti-VEGF medications are now well-established in clinical practice, yet ongoing studies continue to evaluate and compare the efficacy and safety profiles of different drugs.

Materials and methods: A review of literature was conducted using Google Scholar and PubMed databases, focusing on articles published between 2020 and 2025.

Key words: Retinopathy of Prematurity; Laser Coagulation; Bevacizumab; Scleral buckling; Vitrectomy

Introduction

Retinopathy of prematurity (ROP) is a rare ocular disorder that was first described in 1942 by Theodore Terry, who initially termed the condition ‘retrolental fibroplasia’ (RLF) [1]. Despite significant advancements in neonatal care, screening programs, and treatment options, it remains one of the leading causes of childhood blindness worldwide [2].

Pathogenesis:

Vasculogenesis in the retina begins during the fourth month of pregnancy, starting from the optic nerve. On the nasal side, development is completed by the end of the eighth month, while on the temporal side, it is completed about one month after birth. This means that infants born prematurely have large areas of unvascularized retina at the periphery [1, 3].

In the intrauterine environment, oxygen concentration remains below 50mmHg during the second half of the pregnancy. For a premature infant, even room air creates a hyperoxic environment, which is further intensified by the use of supplemental oxygen in incubators. [4]. The increase in blood oxygenation causes vasoconstriction, which damages immature vessels at the border between the vascularised and non-vascularised zones. This halts the physiological development of vessels in the non-vascularised retina. In the hypoxic retina, metabolic disturbances occur, leading to the production of growth factors- most notably VEGF. These growth factors induce neovascularization and the growth of abnormal blood vessels into the vitreous, accompanied by a proliferation of fibrous tissue. Subsequent contraction of the fibrovascular tissue leads to retinal detachment. [5-8].

The Neonatal Oxygenation Prospective Meta-analysis Collaboration showed that lower target oxygen saturation (85–89% vs. 91–95%) reduced the risk of severe ROP but simultaneously

increased mortality and necrotizing enterocolitis. Currently, the European guidelines recommend saturation targets between 90 and 94% [9, 10].

Epidemiology:

Three distinct epidemics of ROP have been described. The first one occurred in the 1940s and 1950s and was attributed to the unregulated use of supplemental oxygen and the absence of appropriate monitoring in neonatal units. The second epidemic began in the 1960s and 1970s and is attributable to advancements in neonatal that improved the survival rates of less mature infants in high-income countries [4].

The third epidemic, which began in the 1990s and continues to present day, primarily affects middle-income and low income countries. In low income countries, survival rates among the most premature infants remain low. In contrast, middle-income countries have seen increased availability of supplemental oxygen therapies, leading to higher survival rates of preterm infants. However, the necessary equipment for oxygen monitoring is often lacking, resulting in unregulated oxygen administration- a key risk factor for the development of ROP [3]. Moreover, in middle-income countries, a growing number of women deliver in healthcare facilities, increasing the likelihood of preterm infants being admitted to neonatal intensive care units. Compounding the issue, screening programs in such countries are often inconsistently implemented, which increases the incidence of severe ROP [11].

In 2019 approximately 25,000 children worldwide became blind due to ROP, with additional 28,000 experiencing severe vision loss and 49,000 suffering from mild vision loss [12].

Between 2016 and 2021 ROP was diagnosed in about 6,2% of premature infants born in Poland [13]. Data indicate that overall ROP incidence is comparable between male and female infants. However, male infants exhibit a higher prevalence of more severe forms of the disease, suggesting a possible association between sex and ROP progression rates [14].

Screening:

ROP Screening Guidelines differ around the World. The major criteria considered are birth weight and gestational age, with additional factors including prolonged oxygen therapy, suboptimal oxygen monitoring, other risk factors, unstable clinical condition, and recommendation from a neonatologist or pediatrician [3]. Guidelines of the Polish Society of Ophthalmology state that infants should be screened if they are born at ≤ 33 weeks of

gestational age, have a body weight of $\leq 1800\text{g}$, or are determined to be at high risk of ROP by a neonatologist. The first examination should be performed during the fourth week after birth [8].

In Poland, between 2016 and 2021 approximately 32.9% of live preterm infants underwent diagnosis towards ROP. A positive diagnosis was made in 18.3% of cases examined [13].

Examination:

The examination should be performed by an ophthalmologist with experience diagnosing ROP. Pharmacological pupil dilation is required, typically achieved with 2-3 doses of 2.5% phenylephrine and 0.5% tropicamide, administered approximately an hour prior to examination. Additionally, local anesthetic eye drops are advised immediately before examination with 0.5% proparacaine solution being the most commonly used medication [15, 16, 17]. Other effective methods of analgesia during eye examination include oral paracetamol, and intranasal fentanyl [18]. The examination is typically performed using a speculum and 20D and 28 D lenses, along with an indenter or a squint retractor [16].

When retinopathy is confirmed, findings should be documented in accordance with the International Classification of Retinopathy of Prematurity. Photographic documentation using fundus cameras is also recommended, as it provides a reference for subsequent examinations [16,19]. Fluorescein angiography and spectral-domain optical coherence tomography can also be of use, especially in more severe cases [20].

Although indirect ophthalmoscopy remains the gold standard for the diagnosis and staging of ROP, recent studies suggest that, combined with digital retina imaging, AI tools could have a complementary role in the future [20].

Follow- up examinations should be scheduled at intervals of 1 to 3 weeks, depending on the severity and progression of retinal changes [16].

Classification:

There are four main components of ROP classification:

1. Staging
2. Location

3. Presence or absence of plus disease

4. Extent of disease, presented as the number of clock hours involved [19].

There are 5 stages of ROP, with Stage I being the least severe.

Stage I: Demarcation line- A thin, fairly flat and white line at junction between vascularized and avascular retina.

Stage II: Ridge- Progression from the demarcation line, which is no longer flat, appears wider and is white or pink in colour

Stage III: Extraretinal neovascular proliferation- Vascular proliferation extends from the retina into the vitreous

Stage IV: Partial retinal detachment

Stage V: Total retinal detachment [21]

Location:

Zone I: A circular area centered on the optic disc, with a radius twice the distance between the optic disc and the macula.

Zone 2: A larger circular area which reaches the ora serrata on the nasal side.

Zone 3: The remaining crescent-shaped temporal retina.

ROP in Zone I is most likely to be aggressive, whereas ROP in Zone III usually is not [4].

Plus disease is a severe form of ROP. It is characterized by abnormal dilation and tortuosity of posterior pole vessels.

Aggressive posterior ROP (AP-ROP) is a severe and rapidly progressing form of ROP. It does not follow the typical staged progression and can worsen quickly to stage 5 disease. It involves plus disease, often with flat neovascularization.

Extent: The nasal side of the right eye corresponds to 3 o'clock, while the nasal side of the left eye corresponds to 9 o'clock [19].

Treatment:

Approximately 10% of infants screened for retinopathy of prematurity (ROP) require treatment. The primary goals of treatment are to prevent vision loss and blindness, while also preserving the retinal architecture [3, 22].

Treatment is necessary in cases of Type 1 ROP, which is defined as:

Zone I: Any stage of ROP with plus disease, or stage 3 ROP without plus disease

Zone II: Stage 2 or 3 ROP with plus disease [16]

In addition, treatment should be considered in the contralateral eye even if it does not meet the diagnostic criteria, provided the fellow eye qualifies for treatment.

Treatment should be started within 72 hours of diagnosis. In cases of aggressive posterior ROP (APROP) treatment should begin as soon as possible due to the rapid progression of the condition [16].

Various substances have also been investigated as potential prophylactic agents. These include vitamin A, vitamin E, propranolol, lipids, caffeine, erythropoietin, dexamethasone superoxide dismutase [23-25].

Cryotherapy

Cryotherapy was established as a treatment for ROP in the 1980s. This method involves applying extremely low temperatures to the avascular retina through the external scleral wall using a metal probe exposed to liquid nitrogen. Cryotherapy effectively halts the abnormal growths in the retina and, at the time, was considered a revolutionary and largely successful intervention. However, its use has since declined due to a relatively high side effect profile [2, 8, 22].

Laser photocoagulation

Laser photocoagulation of the avascular retina stops the production of angiogenic factors by causing a thermal reaction that induces protein denaturation. Degradation of the retinal tissue reduces its oxygen demand, which decreases the stimuli for angiogenic factor production. Laser treatment is currently performed with an infrared diode laser of 1018 nm wavelength, frequency-doubled Nd Yag laser or an argon green laser. Laser burns are spaced less than half the burn width apart, covering the entire avascular retina from the ridge to the ora serrata. In cases of APROP, laser spots are delivered within areas enclosed by flat neovascular loops, sparing the fovea [6, 19].

Laser treatment requires general anesthesia or sedation which can be a factor when choosing between treatment options [26].

Polish Ophthalmological Society guidelines state that diode or argon laser therapy remains the method of choice for ROP treatment [15].

Anti- VEGF treatment:

Anti-VEGF intravitreal injections can be used in monotherapy or in combination with laser treatment [15].

Four different anti-VEGF drugs have reportedly been used: bevacizumab, ranibizumab, aflibercept and conbercept. Bevacizumab is by far the most commonly used one. Treatment with bevacizumab allows for the continued development of peripheral retinal vessels, whereas treatment with laser results in permanent destruction [27]. When compared to laser photocoagulation intravitreal bevacizumab shows similar results [3].

Intravitreal injections can be performed under local anesthesia [26].

Infants receiving laser treatment have an increased risk of developing high myopia. Bevacizumab injections have been linked to adverse neurodevelopmental outcomes in some studies, while others make no such connection. [3, 5, 27]. Recently more studies have focused on ranibizumab and aflibercept as potentially safer and more effective [6].

Surgical options

Surgery can be considered in cases when retinal detachment has occurred. Main surgical options are scleral buckling or vitrectomy.

Scleral buckling is a procedure used to repair retinal detachment. Silicone bands are wrapped over the sclera and sewn into place. The retina is then pressed back into place by the resulting pressure. Excess fluid from under the detached retina can be removed during this procedure by making an additional incision. The scleral buckle should be monitored with appointments at least every 6 months and can be removed if it is too tight, creates other issues or when appropriate to make room for the eye to develop [8]. Anatomical success, meaning successful retinal reattachment vastly varies, ranging from 30% to 100%, mostly depending on staging of ROP. Visual outcomes are often disappointing. Potential side effects include increased intraocular pressure and high myopia together with anisometropia due to axial elongation.

Research has shown scleral buckling to be more successful when combined with laser or anti-VEGF treatment [28, 29].

Lens-sparing vitrectomy is more often used in cases of ROP as compared to lensectomy-vitrectomy to avoid aphakia which hinders the physiological development of the eye and increases the risk of developing glaucoma [30]. Lens sparing vitrectomy is performed by removing the vitreous along with blood and scar tissue through incisions in the sclera. Before, an infusion line is placed to maintain intraocular pressure. Saline solution is used to replace the vitreous. It is a serious and difficult procedure [8]. Anatomical success of the procedure ranges from 19% in Stage 5 ROP to 100% in Stage 4A [30].

Prognosis

Most cases of ROP are mild, do not require treatment and resolve spontaneously. However, it is important to note that preterm birth is in itself a risk factor for ophthalmological issues. Refractive errors including myopia, astigmatism and anisometropia are the most common ophthalmic consequences of ROP and are more severe and begin earlier in infants that needed, and underwent treatment. ROP does not seem to affect visual fields [31]. ROP is also a risk factor for cognitive impairment and intellectual disability, with the risk being higher in more severe stages of ROP [32, 33].

Conclusions

Retinopathy of prematurity is a disease that has been known for over 80 years. Since then, three major epidemics have occurred that differed in causes. Currently ROP is a problem around the world, but most notably in middle-income countries.

Treatments for ROP have evolved over the years. Cryotherapy has revolutionised the treatment of this disease but has become less relevant over the years. Laser photocoagulation and anti-VEGF intravitreal injections are both effective treatments that differ most in their risk profile. Comparison between various anti-VEGF medications and their dosage remains an important avenue for research. Surgical options, including scleral buckling and vitrectomy are reserved for cases of ROP where there has already been a detachment of the retina, but their effects can often be disappointing due to the severity of the disease in some of the cases where they are applied.

Advances in neonatal care can pose a challenge as they facilitate the survival of less developed infants, which is the most important risk factor for ROP. At the same time, they can be part of the solution as supplemental oxygen monitoring is crucial in ROP prevention. Widespread screening allows cases of ROP to be quickly diagnosed and carefully monitored or to swiftly administer treatment.

Although retinopathy of prematurity remains a leading cause of childhood blindness, most cases are mild, do not require treatment and resolve without treatment. In more severe cases, ROP itself, as well as the treatment used, can lead to various ophthalmic and non-ophthalmic consequences.

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