CASE REPORT

# AGGRESSIVE POSTERIOR RETINOPATHY OF PREMATURITY (APROP), TIMELY SCREENING AND APPROPRIATE TREATMENT - CASE REPORT

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**Key words:** retinopathy of prematurity (ROP), anti-VEGF, screening, visual acuity, APROP

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## Abstract

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the retina that is one of the leading causes of blindness in children. In this paper, we describe a case of a premature male child diagnosed with a aggressive posterior form of ROP (APROP) and treated with anti-VEGF injections in both eyes. Ophthalmological monitoring was done during several years of the child's growth. The aim is to highlight the importance of timely screening protocols in order to prevent permanent consequences on visual acuity.

ПРИКАЗ НА СЛУЧАЈ

# ЗАДНА АГРЕСИВНА ПРЕМАТУРНА РЕТИНОПАТИЈА (APROP), НАВРЕМЕН СКРИНИНГ И СООДВЕТЕН ТРЕТМАН - ПРИКАЗ НА СЛУЧАЈ

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## Извадок

Прематурната ретинопатија (РОП) е вазопролиферативно заболување на ретината коепретставува една од водечките причини за слепило кај децата. Во овој труд опишуваме случај на предвреме родено машко дете кое е дијагностицирано со задна агресивна форма на РОП (APROP ) и истото е третирано со примена на анти-VEGF инекции во двете очи. Направен е офталмолошки мониторинг во текот на повеќе години од растот на детето. Целта е да се истакне важноста на навремените скрининг протоколи со цел спречување на трајните последици по видната острина.

## Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the retina that can lead to significant vision loss and even blindness. ROP is one of the leading causes of blindness in children. Globally, ROP is becoming a significant health issue, particularly in regions where premature birth rates are rising, and neonatal care is improving. The exact incidence varies, but worldwide, it's estimated that 15-20% of premature infants may develop ROP to some degree[1]. ROP is a significant concern in North Macedonia. A retrospective study analyzing data from 2010 to 2020 reported that out of 15,825 examinations conducted, screening was performed on 4,518 (11.66%) premature babies. Among these, 580 (12.84%) were diagnosed with active ROP requiring treatment. Treatment modalities included laser photocoagulation for 345 (59.48%) infants and Anti-VEGF therapy for 243 (41.9%) infants[2]. There are several stages of the disease's evolution. APROP (aggressive posterior retinopathy of prematurity) is considered the most severe form. In order to prevent complications such as retinal detachment, cataracts, glaucoma, myopia, strabismus, and amblyopia, protocols have been established worldwide for the screening and treatment of these children. There are several types of treatment, the most commonly used of which are laser photocoagulation and the application of anti-VEGF injections. Regardless of the choice of treatment, regular fundus examinations are essential to ensure that the condition of the fundus does not worsen.

## Case Report

In our case report, we are talking about a premature male baby. He was born at 30 weeks of gestation with a birth weight of 2290 grams. He underwent a consultative examination at the University Clinic for Gynecology and Obstetrics in Skopje, the neonatal intensive care unit. The examination was performed by a pediatric ophthalmologist from the University Clinic for Eye Diseases in Skopje, trained in the examination and treatment of premature infants. The examination was performed at 34 weeks of gestation using an indirect ophthalmoscope and a 28-dioptre magnifying glass, a blepharostat and an indentor. The patient was administered a local anesthetic, tetracaine. During the examination, a very severe form of retinopathy of prematurity, APROP, was diagnosed. An indication for the use of anti-VEGF treatment, i.e. the application of Avastin in both eyes, was established. The application of Avastin, in both eyes, was carried out one day after the diagnosis and indication at the PHI University Clinic for Gynecology and Obstetrics. The procedure was performed under local anesthesia. The application was performed using an insulin needle in the area of 2mm from the limbus, at an angle of 90 degrees, i.e. directed towards the posterior pole of the eye. After the application, antibiotic therapy and a nonsteroidal anti-inflammatory agent were prescribed as per the protocol. A control was performed after 5 days of the application. No side effects or complications were observed. Regular controls were

performed after 2 weeks and every 2 weeks until the 41st gestational week at the PHI University Clinic for Eye Diseases. It was noted that there was no progression, but rather an improvement in the condition of the fundus. By improvement of the condition is actually meant regression of the pathological blood vessels. The prescribed therapy was then discontinued. The next control was performed when the child was 3 months old. An ultrasound examination was performed and a normal finding was noted. The ultrasound was repeated on several occasions, at an interval of 3 months. The ultrasound finding was with a normal finding of the eyeballs. Further examinations were performed in the strabismus office. The child was already 2 years old. Regular check-ups were performed every 6 months until the third year of age. At that time, a fundus examination was performed. The following findings were recorded: PNO at the level of the retina with clear boundaries and color, blood vessels with an orderly flow and lumen, macula lutea with a clear foveolar reflex. In addition to the fundus examination, refraction with cycloplegia (Atropine a 0.5%), refractometry in mydriasis were performed and the results were noted. At that examination, the child had a visual acuity of 0.8 partially in both eyes. The refraction showed a hyperopic form of astigmatism which was then corrected with distance glasses. Visual acuity of 1.0 was achieved with correction in both eyes. Since then, the child has been coming for regular 6-monthly check-ups and he has consistently had a visual acuity of 1.0 with correction in both eyes.

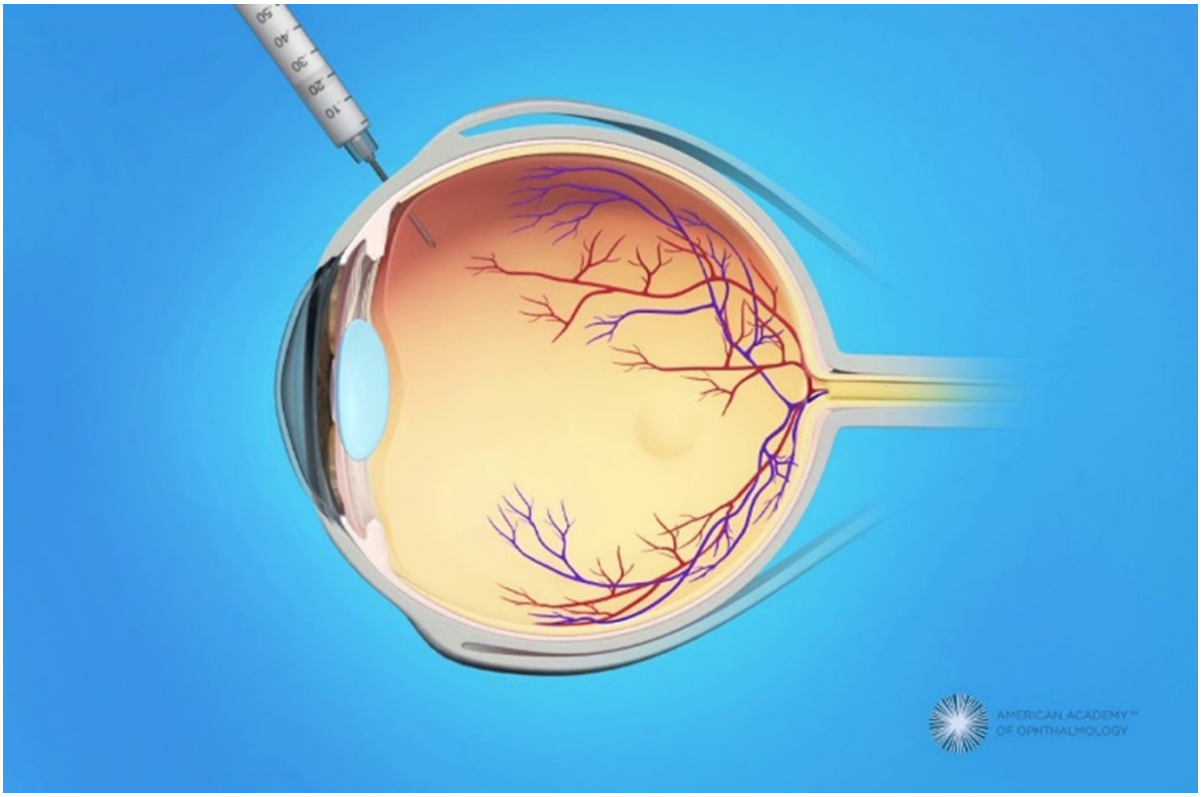


**Figure 1:** Application of anti-VEGF injection
Source: American Academy of Ophthalmology

## Discussion

With the development of intensive care for premature babies, the survival rate of extremely premature babies is increasing. This leads to an increase in the incidence of ROP. Oxygenation, i.e. hyperoxia and hypoxia of the retina, plays a key role in the pathogenesis of the disease. It directly affects vascular endothelial growth factor (VEGF), which in turn causes abnormal growth of pathological blood vessels. The retina is the photosensitive part at the back of the eye that has blood vessels that develop gradually during fetal development. This process should be completed from 36 to 40 weeks of gestation. In premature babies, the process of retinal blood vessel development is incomplete. Blood vessels do not reach the extreme periphery of the retina, leaving an avascular zone that is extremely sensitive to oxygen concentration. Premature babies are placed in incubators with a high concentration of oxygen in neonatal intensive care units. These oxygen concentrations contribute initially to vasoconstriction of the retinal blood vessels, thereby weakening the avascular zones, which at the same time suffer from hypoxia. As a compensatory mechanism for hypoxia, vascular endothelial growth factors are secreted, which lead to the growth of new blood vessels. They are fragile and can leak and bleed, and lead to further complications such as the growth of fibrovascular membranes in the vitreous body. These membranes have the ability to contract and exert traction on the retina. This can lead to retinal detachment and loss of vision[3,4].

There are several stages of disease evolution:

Stage 1 (line of demarcation); the first sign of ROP is the formation of a thin, wavy gray-white line that is approximately parallel to the ora serrata and separates the avascular from the vascular retina. The line is noticeable at the temporal periphery and abnormal branching blood vessels can be seen leading to it.

Stage 2 (ridge); If the disease progresses, the line of demarcation develops into a raised ridge above the level of the retina.

Stage 3 (ridge with extraretinal fibrovascular proliferation); As the disease progresses from stage 2 to stage 3, the ridge acquires a pink color due to fibrovascular proliferation, which advances to the surface of the retina and invades the vitreous. It is accompanied by dilatation and tortuosity of the retinal blood vessels behind the equator. Retinal hemorrhages are common and vitreous hemorrhage may also occur.

Stage 4 (sub-total retinal detachment); occurs after progression of fibrovascular proliferation. The detachment occurs at the extreme periphery and spreads centrally. Typically develops in neonates around 10 weeks of age.

Stage 5 (total retinal detachment)

Plus disease: refers to the severity of the changes in the blood vessels in the retina. There is a worsening of the condition, with the blood vessels becoming tortuous and dilated.

Any of these changes may be located in one of three zones of the fundus: zone 1 - posterior pole, zone 2 - mid-periphery, and zone 3 - far periphery.

The most severe form is considered to be the APROP form. It is characterized by rapid and severe progression compared to other forms of ROP.

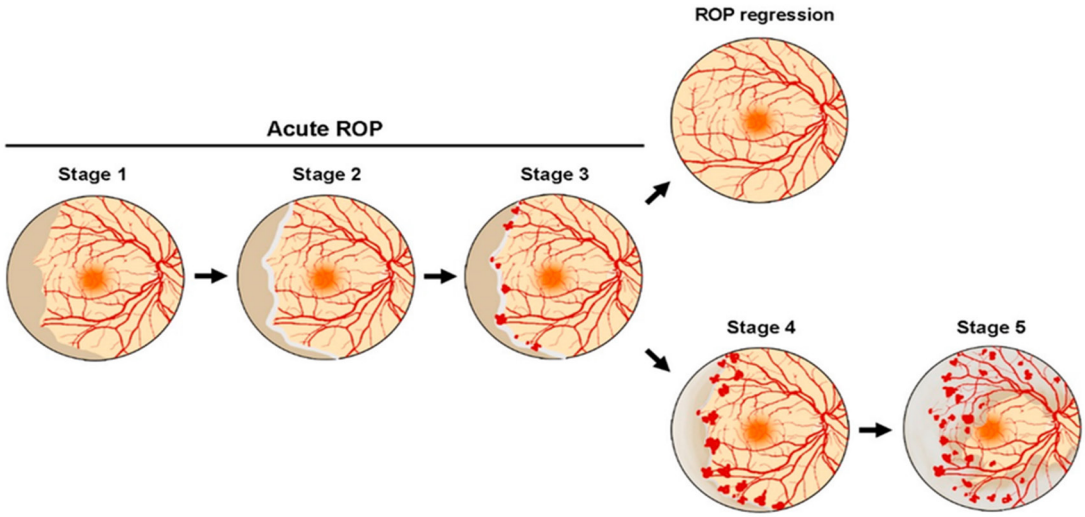


**Figure 2:** Stages of retinopathy of prematurity
Source: https://www.researchgate.net/figure/Schematic-representation-of-retinopathy-of-prematurity-ROP-stages-Stage-1-is_fig1_361838879

Rapid progression occurs within a few days to weeks, unlike the more common forms that progress more slowly, over a few weeks to months. Changes in the fundus are at the posterior pole and affect the center for clear vision – the macula. There is pronounced tortuosity and dilation of the blood vessels at the posterior pole, i.e. plus disease. These blood vessels are fragile, disorganized and prone to leakage and bleeding. This leads to the development of macular edema and the formation of scars on the retina. Risk factors for the occurrence of this aggressive form include low birth weight, especially below 1000 grams, gestational week, below 27 weeks, fluctuation of oxygen concentration in neonatal intensive care, infections and other medical complications, as well as race (black) and genetic factors.[5][6]

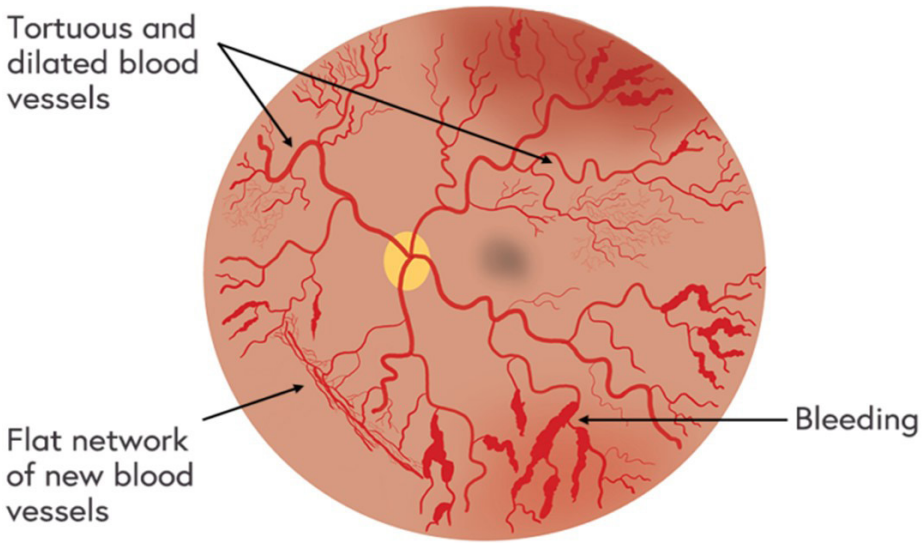


**Figure 3:** Aggressive posterior retinopathy of prematurity APROP
Source: https://www.futurelearn.com/info/courses/retinopathy-of-prematurity-practical-approaches-to-prevent-blindness/0/steps/90569

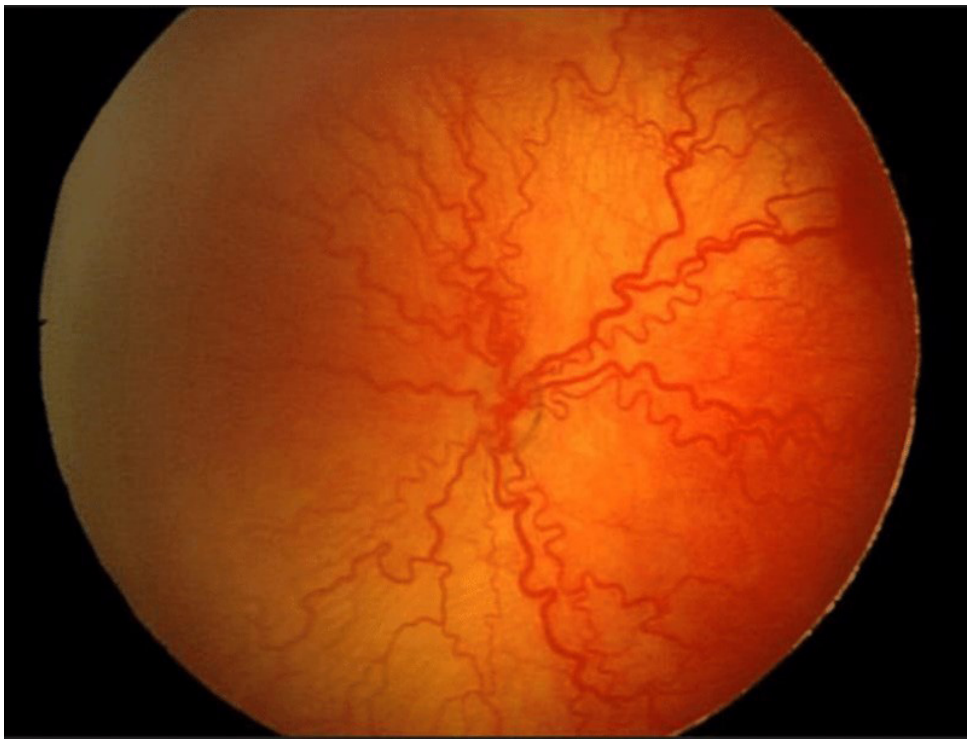

**Figure 4:** APROP
Source: https://www.futurelearn.com

The prognosis of APROP depends on early detection and early treatment. In terms of therapeutic modalities, the most widely used worldwide are laser photocoagulation and the application of anti-VEGF injections. Laser photocoagulation limits the already occurring changes in the periphery of the retina, while anti-VEGF treatment acts directly on VEGF receptors and inhibits the growth of new blood vessels[7]. Early treatment helps preserve central vision, although some children develop refractive errors such as myopia and astigmatism[8].

In general, complications of ROP can be divided into two groups, i.e. complications that occur soon after the diagnosis of ROP, and complications that occur several months to years later.

The American Academy of Pediatrics, the American Academy of Ophthalmology, and the American Association of Pediatric Ophthalmology and Strabismus have established direct guidelines for screening these patients. According to them, every premature baby born under 30 weeks of gestation and with a birth weight of less than 1500g should be examined with indirect ophthalmoscopy of dilated pupils[9, 10].

The purpose of screening for ROP is: early detection, identification of risk factors, monitoring of progression, determining appropriate treatment and preventing blindness. Early detection allows for the recognition of babies at risk and establishing a diagnosis when timely treatment is crucial. Timely treatment before the disease progresses to permanent stages prevents irreversible damage to the retina, thereby preserving and maintaining the normal structure and function of the retina for further complete functionality of the organ of vision[11].

## Conclusion

Retinopathy of prematurity as a disease of modern and advanced medicine is one of the leading causes of blindness in children worldwide. The occurrence of ROP depends directly on the neonatal intensive care centers, the experience of the pediatric ophthalmologist, as well as the structural predispositions and factors of the eye for the development of the disease. The pathogenesis of ROP involves a delicate balance between oxygen exposure, premature retinal vascular development and excessive response to hypoxia. The most complex moment is the cellular mechanisms that lead to this condition, and we can directly influence them only through timely detection of children at risk and timely examination and treatment. Screening is a method that allows for multidisciplinary cooperation in order to provide care and a chance for excellent vision for the premature baby. However, we need experienced and professional pediatric ophthalmologists who, in suspicious cases, make the assessment and decision for treatment, and of course monitoring after treatment.

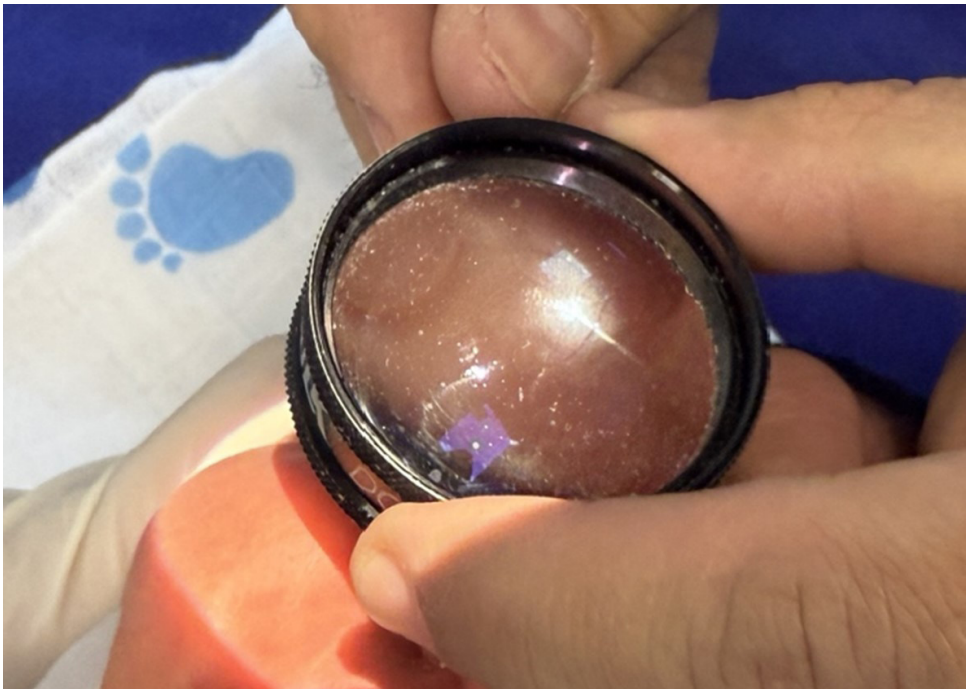

**Figure 5:** Fundus examination with indirect ophthalmoscope, 28-dioptre magnifying glass and indentor

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