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Changes in the nomenclature of ROP according to the International Classification of Retinopathies of Prematurity – a current review of the literature

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ABSTRACT

Introduction: The International Classification of Retinopathy of Prematurity (ICROP) is a consensus that establishes a standard nomenclature for the classification of retinopathy of prematurity (ROP). Initially published in 1984, the classification was expanded in 1987 and again in 2005. In 2019, the revised ICROP was introduced. The third edition (ICROP3), first presented in June 2021, represents a further step in detailing the systematization of knowledge, based on new observations of lesions that emerged during the use of new therapies, such as intraocular anti-vascular endothelial growth factor (anti-VEGF), which result in regression and regeneration of retinal vascularization. These therapies have coincided with the advent of modern imaging methods in ophthalmology. The authors present changes in ROP nomenclature in response to the newly observed and described retinal-vascular lesions in active ROP and in states of ROP regression.

Materials and methods: The new findings and principles of ICROP3, grounded in evidence-based medicine and expert consensus, address the development of new diagnostic and therapeutic methods and new clinical manifestations noted by numerous researchers in the literature.

Results: The new ROP nomenclature retains many of the existing terms while refining and adding new elements to the classification, including posterior zone II, the introduction of the term "notch", subcategories for stage 5, the abandonment of the term "aggressive posterior retinopathy of prematurity" (AP-ROP) in favor of "aggressive retinopathy of prematurity" (A-ROP), and updated descriptions of the course of reactivation and regression. Continued advancements in the science and understanding of ROP lesions will lead to future improvements and updates in this area of ophthalmology.

Conclusions: This presentation of the new classification aims to enhance ophthalmologists' knowledge of ROP classification. It can improve the quality and standardization of ROP treatment by expanding preventive testing and improving evaluations in the clinical care of premature infants.

Keywords: international classification of retinopathy of prematurity (ROP); changes in ROP nomenclature; standardization of ROP treatment.

INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative disease of immature retinal vessels that affects prematurely born infants. The clinical manifestations of ROP range from spontaneous regression to retinal detachment, which in advanced forms can lead to significant visual impairment or even blindness [1]. The primary issue is the incomplete vascularization of the retina, which begins at 13 weeks of gestation and continues until about 36–40 weeks of fetal age [2]. According to global projections, the incidence of ROP in premature infants is steadily increasing. Data from various centers in Europe show a wide range of ROP diagnosis and treatment rates, from a low of 9.4% in Switzerland to a high of 64.1% in Portugal. In recent years, the rising frequency of ROP diagnosis has been closely linked to the tightening of diagnostic criteria (WINROP and G-ROP algorithms), a higher number of low-birth-weight and extremely low-birth-weight preterm infants, and a declining percentage of full-term live births [3]. Despite improved survival rates for preterm neonates, there is a lack of uniform neonatal care quality globally, leading to delays in ROP diagnosis and increased morbidity among preterm infants [1].

In 1984, to standardize diagnostic management, improve ROP outcomes, and enhance the quality of care, the first multicenter clinical trial introduced the International Classification of Retinopathy of Prematurity (ICROP), initiating ROP screening and treatment. In 1987, the ICROP2 guidelines were expanded to include retinal detachment [4]. Over the following decades, until 2005, this classification was further expanded and reexamined to account for therapeutic advancements and the emergence of new clinical manifestations at different stages of ongoing treatment [5].

The third edition of the International Classification of Retinopathy of Prematurity (ICROP3) emerged as a response to the subjectivity and excessive room for individual interpretation by ophthalmologists regarding some findings defined by ICROP, the development of new ophthalmic imaging methods, and the introduction of anti-vascular endothelial growth factor (anti-VEGF) therapies. These factors have posed new challenges in recognizing and describing the clinical signs characteristic of ROP regression and reactivation. Additionally, it is noteworthy that the course of ROP in some regions of the world, where access to modern medical care is limited, has not been adequately covered in previous classification systems [6, 7].

RETINOPATHY OF PREMATURITY ZONES – NEW CHARACTERISTICS

Retinal vascular lesions and abnormalities in ROP are classified based on their location, described in zones I, II, and III, whose definitions remain consistent with previous ICROP guidelines. The new classification introduces further detail in an area located peripherally from the boundaries of zone I and extending deep into zone II by 2DD (disc diameter; the diameter of the optic disc), which the ICROP3 committee defined as posterior zone II. This allows for the identification and differentiation of this particular retinal area, where the presence of lesions or abnormalities may suggest diseases other than ROP.

In practice, to estimate the temporal extent of zone I, a 28 D (diopter) lens can be used by positioning the nasal portion of the optic disc at the border of the visual field, with the zone I border located at the temporal border of the visual field. It is also important to consider that in retinal imaging, the macular fovea may not be clearly visible in premature infants before 39 weeks of postmenstrual age [2, 8, 9].

The New ROP Nomenclature Committee has introduced the term "notch" into the classification. It is recommended to use this term to describe the progression of ROP lesions extending 1–2 clock hours along the horizontal meridian into a zone more posterior than the rest of the lesions in ROP [2] (Fig. 1).

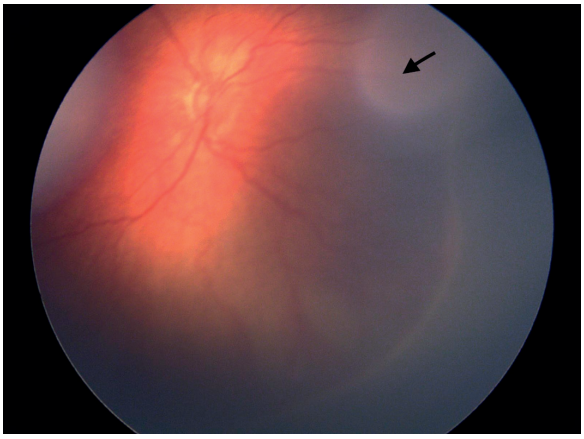

FIGURE 1. Retinopathy of prematurity with notch sign. The arrowhead points to the notch

PLUS AND PRE-PLUS DISEASE

An important aspect of the classification and description of ROP is the term "plus disease" (Fig. 2). This term was introduced into the ROP nomenclature in 1982 and refers to the dilatation and marked tortuosity of the vessels in the posterior pole of the retina. It serves as a prognostic factor, indicating a potentially rapid progression of the disease [5, 10]. In the past, plus disease was characterized by additional abnormalities such as dilatation of the iris vessels, poor pupillary dilation during mydriasis, or dilatation of the peripheral retinal vessels with vitreous body opacification [11]. However, such features are no longer required to diagnose plus disease; they simply suggest an advanced course of ROP [2].

In 2005, ICROP introduced the term "pre-plus disease" to describe abnormal dilatation and tortuosity of the retinal vasculature, though insufficient to diagnose plus disease [5].

Currently, ICROP continues to recommend using the terms "plus disease" and "pre-plus disease". However, it emphasizes that retinal vascular lesions in ROP represent a spectrum rather than distinct, isolated groups, suggesting that ROP should define the condition of zone I vessels rather than focusing on vessels in narrow-angle images. Furthermore, the number of quadrants containing retinal ROP vascular lesions should be key in establishing such a definition [4, 5, 12, 13].

In clinical practice, assessing disease severity may also involve other factors, including clinical and demographic risk factors, the method of investigation, pathological zones, and the rate of disease progression [2].

ACUTE STAGES OF RETINOPATHY OF PREMATURITY (1–3)

The development of retinal blood vessels in term newborns occurs between approx. 16–36 weeks of gestation on the nasal side and up to 40 weeks on the temporal side of the retina [14]. In infants born prematurely, this process is incomplete at birth, and retinal vascularization remains unfinished. In the absence of ROP-specific lesions, ICROP recommendations suggest referring to this condition as "incomplete vascularization" with an associated zone (e.g., "incomplete vascularization in zone 2"). According to ICROP, this terminology is more accurate than describing the condition as "no retinopathy" or "immature retina" [2] (Fig. 2).

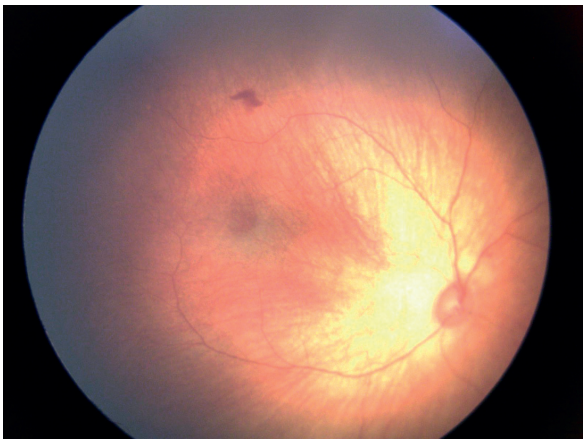

FIGURE 2. Retinopathy of prematurity and incomplete vascularization of retina

In the presence of ROP-specific lesions, the stage of the disease should be evaluated based on the characteristics of each stage. If multiple stages of ROP are present in 1 eye, the most advanced stage should be considered. The stages are described as follows:

- stage 1 – "demarcation line": the hallmark of this stage is the presence of a demarcation line, a thin, flat, and white structure that separates the non-vascularized from the vascularized retina (without this, ROP cannot be diagnosed as stage 1) – Figure 3;
- stage 2 – "ridge": this stage is characterized by the presence of a ridge, which is white to pink in color and arises from the demarcation line [15];
- stage 3 – "extraretinal neovascular proliferation": stage 3 is diagnosed when neovascular proliferation extends from the ridge toward the vitreous body and continues along its posterior surface [2].

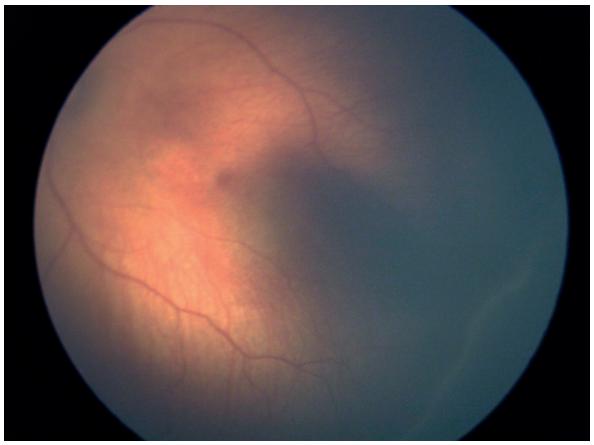

FIGURE 3. Retinopathy of prematurity 2 and demarcation line

CHARACTERISTICS OF THE AGGRESSIVE STAGE OF RETINOPATHY OF PREMATURITY (A-ROP, AP-ROP)

The rapidly progressive form of ROP, typically confined to zone I or posterior zone II, was initially referred to as "rush disease" or "aggressive posterior retinopathy of prematurity" (AP-ROP), a term introduced into the nomenclature by ICROP in 2005 [5]. However, these terms and the earlier definitions of this form of ROP have evolved significantly. Recent advancements in ophthalmology and a greater understanding of ROP have shown that this form of retinopathy is not limited to the most immature preterm infants, nor is it confined exclusively to the posterior retina, as previously thought [16].

For this reason, ICROP now recommends that lesion location should not be a diagnostic criterion for this form of ROP. Instead, the disease's rate of progression and the presence of vascular abnormalities in the retina should serve as the key diagnostic factors. Consequently, the term has been officially changed from AP-ROP to "aggressive retinopathy of prematurity" (A-ROP) [2].

To correctly diagnose A-ROP, the disease must be characterized by the rapid development of pathological neovascularization, accompanied by "plus" disease, without progression through the typical stages of ROP (Fig. 4). Additionally, early signs of A-ROP may include abnormalities such as arteriovenous leakage or, in extreme cases, complete loss of retinal vascularization (Fig. 5).

It is important to note that some forms of A-ROP may initially present with seemingly featureless vascularization, followed by the appearance of an atypical network of flat neovascularization. This can make it difficult to visualize these pathological vessels during ophthalmoscopy. In such cases, using higher magnification (e.g., a 20-D lens) or fluorescein angiography may be helpful. Moreover, the extraretinal neovascularization characteristic of classic stage 3 ROP may also be observed in eyes with A-ROP [17].

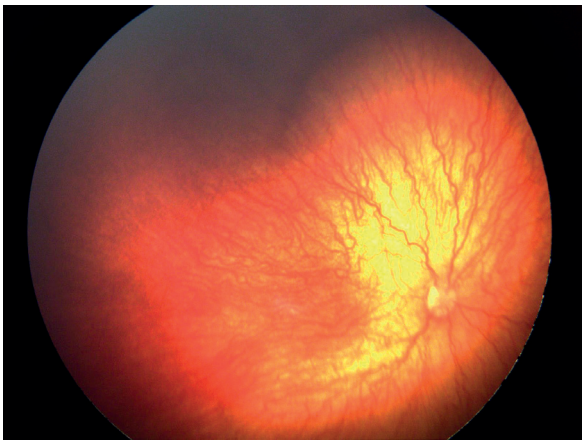

FIGURE 4. Aggressive retinopathy of prematurity with incomplete retinal vascularization and plus sign

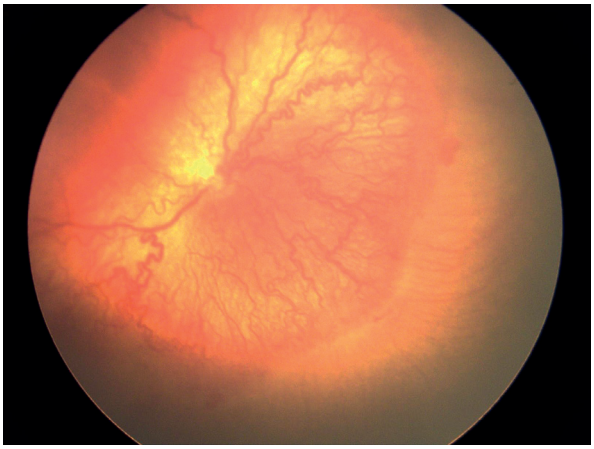

FIGURE 5. Aggressive posterior retinopathy of prematurity and "plus" disease

CHARACTERISTICS OF STAGE 4 – PARTIAL RETINAL DETACHMENT

Stage 4 is characterized by a partial retinal detachment, which may involve the central fovea of the macular area, visible on optical coherence tomography (OCT), leading to a loss of vasculature detail and/or atrophy of the retinal pigment epithelium. It may also present a "ground-glass appearance" in the adjacent retina. Stage 4 can manifest in 2 forms: exudative, where the detachment is convex, focal, and self-limiting,

or tractional, which is associated with the formation of fibrovascular tissue, opacification of the vitreous body, and sometimes lipid or subretinal hemorrhage. Additionally, stage 4 retinal detachment can occur in both treated and untreated eyes, resulting in a broad range of clinical presentations [2].

CHARACTERISTICS OF STAGE 5 – RETINAL DETACHMENT AND NEW CLASSIFICATION BREAKDOWN

One of the updates introduced in ICROP3 is the subcategorization of stage 5 ROP, aimed at improving classification through bedside diagnosis. When fibrosis prevents the visualization of the posterior pole, B-scan ultrasound should be used to assess the degree of retinal detachment.

Stage 5 ROP, representing complete retinal detachment, is now defined in 3 configurations [18, 19]:

- stage 5A: the optic nerve disc is visible on ophthalmoscopy;
- stage 5B: the optic nerve disc is not visible due to the presence of extra-lens secondary fibrovascular tissue or funnel-shaped retinal detachment;
- stage 5C: the changes seen in stage 5B are accompanied by abnormalities in the structures of the anterior segment of the eye (e.g., anterior lens ectopia, shallowing of the anterior chamber, adhesions between the iris and lens capsule, or between the lens capsule and endothelium, central corneal haze, or a combination of these features) – Figure 6.

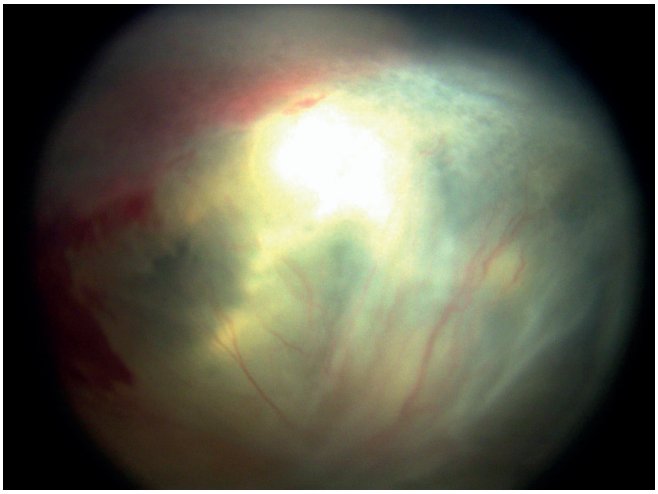

FIGURE 6. Retinopathy of prematurity 5 and complete detachment of the retina

Based on the effects of vitrectomy procedures performed between 2004–2020, a study titled "Structural outcome after surgery for stage 5 retinopathy of prematurity based on the new international classification: ICROP 3", authored by Mano et al., was conducted. The study analyzed the outcomes of surgery on 54 eyes with stage 5 ROP, categorized according to the new 3-stage classification. It was found that complete retinal apposition was achieved in 16 eyes with stage 5A and 13 eyes with stage 5B, while 3 patients in stage 5C were considered inoperable [20]. Additionally, the study highlighted that postoperative complications were strongly correlated with the stage of ROP diagnosis, with stage 5B being significantly more common than stage 5A. The study concluded that the categorization of stage 5 ROP, as recommended by ICROP3, is a good predictor of postoperative success [21].

RETINOPATHY OF PREMATURITY REGRESSION STAGE – CHARACTERISTICS OF CLINICAL RETINAL AND VASCULAR CHANGES

The introduction of intravitreal anti-VEGF injections as a treatment option for ROP has created the need for an updated classification due to the differences in the characteristics and duration of ROP regression following anti-VEGF therapy compared to laser therapy [7]. According to ICROP3, the concept of regression is defined as the involution and resolution of the disease, along with the reduction and fading of neovascular tissue. The ICROP3 also distinguishes between spontaneous regression and regression following ROP therapy [2].

After both anti-VEGF therapy and laser photocoagulation, regression of ROP lesions begins with the occlusion of vascular abnormalities. In the case of anti-VEGF injections, this process occurs much more rapidly, often within 1–3 days, compared to the slower progression seen in spontaneous regression or after laser photocoagulation. Signs of regression may include a reduction in tortuosity and vasoconstriction in "plus" disease, vascularization of previously avascular areas of the retina, involution of the lens choroidal membrane, resolution of intraretinal hemorrhages, and improved clarity of the optic media [22].

The vascularization of previously avascular areas may be either complete or incomplete. In cases of incomplete vascularization, this condition is termed "persistent avascular retina" (PAR), which can occur in both peripheral and posterior regions of the retina. When describing PAR, it is important to specify its exact extent and location [2].

REACTIVATION OF RETINOPATHY OF PREMATURITY LESIONS

Reactivation can occur after complete or incomplete regression of retinovascular ROP lesions, typically between 37–60 weeks of postmenstrual age following anti-VEGF injection. It is defined as the recurrence of acute-phase ROP features and is more frequent after anti-VEGF therapy than after spontaneous regression or total laser photocoagulation [23]. Symptoms of reactivation range from the appearance of a new self--limiting demarcation line to the recurrence of "plus" disease in stage 3 ROP. Notably, ICROP3 highlights that reactivation does not always follow the expected sequence of ROP stages.

Changes associated with reactivation include recurrent vasodilation, tortuosity, extraretinal neovascularization, and hemorrhages in the anterior region of extraretinal vessels [24]. When describing reactivation, ICROP recommends using the term "reactivated" and specifying the location (zone) and stage of ROP lesions.

For example, a demarcation line during reactivation should be described as "reactivated stage 1". In cases of reactivated stage 2, where multiple ridges are present, the term "reactivated" should apply to the more anterior, and typically more active, ridge.

Reactivation progressing to stage 4 or 5 ROP is usually associated with changes in vitreous density, opacification, fibrous shrinkage, or retinal defects [2, 25, 26].

LONG-TERM COMPLICATIONS

Prematurely born children, including those who have not developed ROP, can experience various ocular abnormalities and long-term complications [27, 28]. According to ICROP, retinal detachment in the absence of other symptoms of ROP should not be considered a result of reactivation but rather as a complication, such as retinal detachment due to chronic traction or PAR. Persistent avascular retina, which lacks sufficient vascularization, is susceptible to attrition, degeneration, retinal loss, and macular anomalies [29, 30].

CONCLUSIONS

Advances in diagnostics, new therapeutic approaches such as anti-VEGF injections, and modern imaging methods have significantly expanded the understanding of ROP, creating a need to update the nomenclature and classifications required for accurate and uniform documentation of the disease. The publication of ICROP3, grounded in evidence-based literature and expert consensus, addresses this need by retaining many of the previously established terms while introducing new classification elements, including posterior zone II, the term "notch", subcategories in stage 5, the shift from AP-ROP to A-ROP, and updated descriptions of reactivation and regression. However, it is crucial to recognize that as scientific knowledge of ROP continues to evolve, further refinements and updates in this area of ophthalmology will be necessary in the future.

REFERENCES

1. Dogra MR, Katoch D, Dogra M. An update on retinopathy of prematurity (ROP). Indian J Pediatr 2017;84(12):930-6.
2. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A, et al. International Classification of Retinopathy of Prematurity, Third Edition. Ophthalmology 2021;128(10):e51-68.
3. Modrzejewska M, Bosy-Gąsior W. Most up-to-date analysis of epidemiological data on the screening guidelines and incidence of retinopathy of prematurity in Europe – a literature review. J Clin Med 2023;12(11):3650.
4. International Classification of Retinopathy of Prematurity Committee for Classification of Late Stages of ROP. An international classification of retinopathy of prematurity: II. The classification of retinal detachment. The International Committee for the Classification of the Late Stages of Retinopathy of Prematurity. Arch Ophthalmol 1987;105(7):906-12.
5. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005;123(7):991-9.
6. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med 2011;364(7):603-15.
7. Stahl A, Lepore D, Fielder A, Fleck B, Reynolds JD, Chiang MF, et al. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. Lancet 2019;394(10208):1551-9.
8. Chiang MF, Thyparampil PJ, Rabinowitz D. Interexpert agreement in the identification of macular location in infants at risk for retinopathy of prematurity. Arch Ophthalmol 2010;128(9):1153-9.
9. De Silva DJ, Cocker KD, Lau G, Clay ST, Fielder AR, Moseley MJ. Optic disk size and optic disk-to-fovea distance in preterm and full-term infants. Invest Ophthalmol Vis Sci 2006;47(11):4683-6.
10. Quinn GE, Schaffer DB, Johnson L. A revised classification of retinopathy of prematurity. Am J Ophthalmol 1982;94(6):744-9.
11. The Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. Arch Ophthalmol 1984;102(8):1130-4.
12. Gelman SK, Gelman R, Callahan AB, Martinez-Perez ME, Casper DS, Flynn JT, et al. Plus disease in retinopathy of prematurity: quantitative analysis of standard published photograph. Arch Ophthalmol 2010;128(9):1217-20.
13. Kim SJ, Campbell JP, Kalpathy-Cramer J, Ostmo S, Jonas KE, Choi D, et al. Accuracy and reliability of eye-based vs quadrant-based diagnosis of plus disease in retinopathy of prematurity. JAMA Ophthalmol 2018;136(6):648-55.
14. Provis JM. Development of the primate retinal vasculature. Prog Retin Eye Res 2001;20(6):799-821.
15. Lepore D, Molle F, Pagliara MM, Baldascino A, Angora C, Sammartino M, et al. Atlas of fluorescein angiographic findings in eyes undergoing laser for retinopathy of prematurity. Ophthalmology 2011;118(1):168-75.
16. Shah PK, Narendran V, Saravanan VR, Raghuram A, Chattopadhyay A, Kashyap M, et al. Fulminate retinopathy of prematurity – clinical characteristics and laser outcome. Indian J Ophthalmol 2005;53(4):261-5.
17. Sanghi G, Dogra MR, Dogra M, Katoch D, Gupta A. A hybrid form of retinopathy of prematurity. Br J Ophthalmol 2012;96(4):519-22.
18. Gadkari SS, Deshpande M, Kulkarni S. Minimally fibrotic stage 5 ROP: a clinical prognostic factor in eyes undergoing vitrectomy for stage 5 retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol 2016;254(7):1303-9.
19. Ozsaygili C, Ozdek S, Ozmen MC, Atalay HT, Yeter DY. Preoperative anatomical features associated with improved surgical outcomes for stage 5 retinopathy of prematurity. Retina 2021;41(4):718-25.
20. Mano F, Iwahashi C, Kuniyoshi K, Kusaka S. Structural outcome after surgery for stage 5 retinopathy of prematurity based on the new international classification: ICROP 3. Retina 2022;42(10):1950-7.
21. Promelle V, Milazzo S. Rétinopathie du prématuré. J Fr Ophtalmol 2017;40(5):430-7.
22. Vural A, Ekinci DY, Onur IU, Hergünsel GO, Yiğit FU. Comparison of fluorescein angiographic findings in type 1 and type 2 retinopathy of prematurity with intravitreal bevacizumab monotherapy and spontaneous regression. Int Ophthalmol 2019;39(10):2267-74.
23. Dogra MR, Vinekar A. Role of anti-vascular endothelial growth factor (anti-VEGF) in the treatment of retinopathy of prematurity: a narrative review in the context of middle-income countries. Pediatric Health Med Ther 2023;14:59-69.
24. Wallace DK, Dean TW, Hartnett ME, Kong L, Smith LE, Hubbard GB, et al. A dosing study of bevacizumab for retinopathy of prematurity: late recurrences and additional treatments. Ophthalmology 2018;125(12):1961-6.
25. Yonekawa Y, Thomas BJ, Thanos A, Todorich B, Drenser KA, Trese MT, et al. The cutting edge of retinopathy of prematurity care: expanding the boundaries of diagnosis and treatment. Retina 2017;37(12):2208-25.
26. Kondo H, Arita N, Osato M, Hayashi H, Oshima K, Uchio E. Late recurrence of retinal detachment following successful vitreous surgery for stages 4B and 5 retinopathy of prematurity. Am J Ophthalmol 2009;147(4):661-6.e1.
27. Coats DK, Miller AM, Hussein MAW, McCreery KM, Holz E, Paysse EA. Involution of retinopathy of prematurity after laser treatment: factors associated with development of retinal detachment. Am J Ophthalmol 2005;140(2):214-22.
28. Bowl W, Lorenz B, Stieger K, Schweinfurth S, Holve K, Andrassi-Darida M. Fundus-controlled dark adaptometry in young children without and with spontaneously regressed retinopathy of prematurity. Transl Vis Sci Technol 2019;8(3):62.
29. Uner OE, Rao P, Hubbard GB3rd. Reactivation of retinopathy of prematurity in adults and adolescents. Ophthalmol Retina 2020;4(7):720-7.
30. Hamad AE, Moinuddin O, Blair MP, Schechet SA, Shapiro MJ, Quiram PA, et al. Late-onset retinal findings and complications in untreated retinopathy of prematurity. Ophthalmol Retina 2020;4(6):602-12.