ORIGINAL ARTICLE

Retinopathy of Prematurity Part I

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SUMMARY

Retinopathy of prematurity (ROP) is a disease that affects immature vasculature in the eyes of premature babies that potentially leads to blindness. Authors describe incidence, risk factors, pathophysiology and international classification of retinopathy of prematurity (ICROP).

Key words: retinopathy of prematurity, incidence, pathophysiology, international classification

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INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the immature retina, which primarily afflicts babies born before the 32nd week of gestation, with a birth weight of less than 1 250 g. At present it remains one of the main causes of blindness and low-vision in children in developed countries, and it is estimated that in 2010 approximately 20 000 children worldwide lost their sight or suffered severe visual impairment as a consequence of ROP (2).

History

Since 1942, when Terry first described proliferation of the retina behind the lens and coined the term retrolental fibroplasia (22), great progress has been made thanks to diagnostic and therapeutic advances in neonatology. In the 1950s, use of incubators was begun for the treatment of premature babies. Over the 10 years period from 1943-53, approximately 7 000 newborn infants lost their sight as a consequence of ROP. Because oxygen therapy was considered to be the cause of blindness, this treatment was subsequently markedly reduced, which brought about a reduction in the number of ROP, but also an increase in mortality (1, 14). Concentration of oxygen was monitored from 1970 onwards, incubators were technically improved, the lives of very immature children were saved and the incidence of ROP again increased, to the extent of a second epidemic of ROP. An improvement in the prognosis of children quo ad visum did not arrive until after 1980, with the introduction of cryopexy and subsequently diode laser coagulation of the retina, and in recent years the use of anti-growth factors has been added to the therapy of ROP.

Incidence

The number of prematurely born children is constantly growing. The age of pregnant women is ever increasing, and with it the risk of health complications in pregnancy, and the number of artificial fertilization is also increasing. Statistically approximately 7.5% of children are born prematurely in Slovakia (11). Approximately 400 children per year are born very prematurely, i.e. before the 28th week of gestation. The incidence of retinopathy of prematurity is indirectly proportional to birth weight and the gestation age of the child. The total incidence of any stage of ROP in children with a birth weight from 1 000-1 250 g has been stated at 34%-60%, in children with a birth weight of less than 1 000 g 53%-88% (17, 19). Severe forms of retinopathy of prematurity occur primarily in children born before the 28th week of gestation and with a birth weight of less than 750 g. With improvement in neonatal care and better understanding of the pathogenesis and risk factors in highly developed countries (North America and Western Europe), the incidence of retinopathy has declined, and occurs primarily in very immature children born before the 26th week of gestation (15), with incidence stated within the range of 5-8% (7). In medium-developed countries – former countries of the Eastern Bloc as well as several countries in Latin America, Asia, a “third epidemic” of ROP later began, in which more severe forms of ROP occur also in larger and more mature children, born between the 28th an 31st weeks of gestation (15), incidence reaches approximately 30%. There may be several reasons for this: the number of premature births has increased, there are insufficient financial resources in neonatology, there is a lack of or insufficiently implemented and developed screening programme and treatment, poor level of informedness and a lack of specialised providers. In very undeveloped countries (parts of Asia and sub-Saharan Africa), blindness as a result of retinopathy of prematurity is practically unknown, since the majority of prematurely born children do not survive the period in which the severe form of ROP would develop (5, 9).

Risk factors

Retinopathy of prematurity is a multifactorial disorder and its main risk factors are birth weight below 1 250 g and a gestation age of less than 28 weeks. A very important factor for the development of the disorder is oxygen therapy and the related changes of oxygen concentration in the blood. Predisposing factors are considered to include respiratory distress syndrome, presence of pneumopathy and chronic lung disease, anaemia and numerous transfusions, sepsis, surgery under general anaesthesia and intraventricular haemorrhage. Retinopathy of prematurity also occurs more frequently upon multiple pregnancy.

Development of vascular system of retina and pathogenesis of ROP

The development of the vascular system of the retina links to the physiological embryogenesis of the vascular

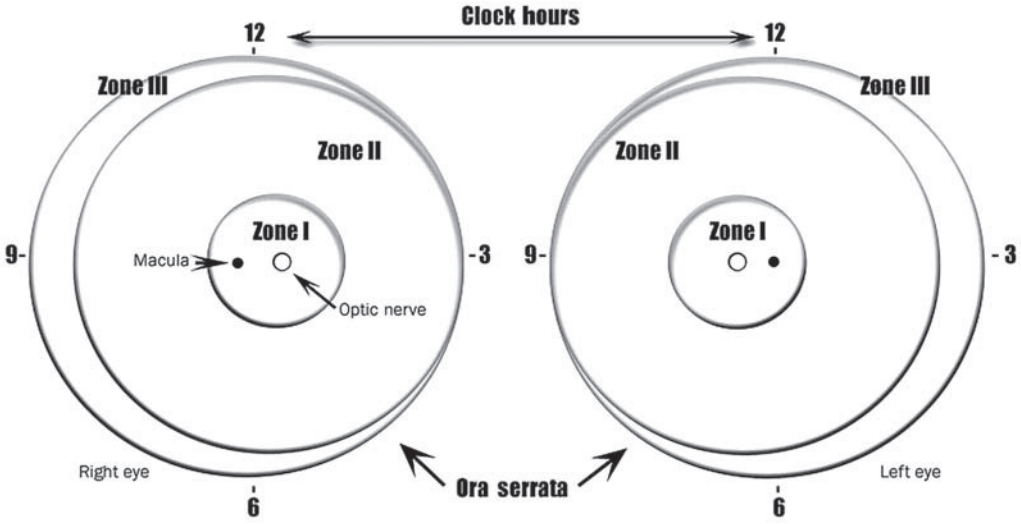

Fig. 1 Schema of retina of right and left eye, illustrating the bordering of the zones and numbers of clock hours used for description of the localisation and extent of changes upon ROP. Zone II is further divided into the central and posterior part, which is adjacent to zone I, and the peripheral part. Zone III is located only in the temporal part of the retina.

system of the eye. The arteria centralis retinae starts from the disc of the optic nerve and progressively grows to the periphery of the retina. The capillaries reach the ora serrata nasally (where the retina is shorter) around the 32nd--36th week of gestation, temporally under physiological circumstances it does not grow up to the ora until the time around the birth, between the 38th and 42nd weeks of gestation. In premature infants, vascularisation of the retina is therefore not completed, and a variously sized part of the retina is avascular. Development of the vascular system takes place in two mutually connected phases.

1. Vasogenesis – early phase, which begins before the 14th gestation week of pregnancy (10), when the primary capillaries of the central superficial plexus originate from the precursor vascular cells of mesenchymal origin, and subsequently grow from the disc of the optic nerve (DON) and form the 4 main arcades of the posterior retina – arcades de novo. This phase is independent of the metabolic requirements and hypoxia induced by VEGF (vascular endothelial growth factor). Vasculogenesis, which is considered completed around the 21st week of gestation, is generally overlapped by the subsequent second phase.

2. Angiogenesis begins around the 17th week of gestation (10). The superficial plexus and deep capillary plexus are formed from the pre-existing capillaries, density of the capillaries of the central retina progressively increases in the area of the incipient fovea (25th-26th week of gestation), and the other retinal capillaries are completed. In this period, the metabolic activity of the retinal neurones increases as a consequence of maturation of the retina, which leads to physiological hypoxia of the retina, with induction of the formation of vascular endothelial growth factor (VEGF) in the astrocytes and Müller cells (16, 21). The new capillaries bring oxygen and nutrition to the maturing retina, with a subsequent decline in the level of VEGF. Physiological hypoxia is the main initiating factor in vascularisation of the retina and astrocytes realise this by means of VEGF (8). This phase is dependent – driven by hypoxia induced by VEGF.

In the case of premature birth there is a drastic change from the intrauterine environment, suddenly the supply of growth factors and nutrient substances from the mother's body, such as IGF-1 (insulin-like growth factor-1) and PUFA (omega-3 polyunsaturated fatty acids) is cut off. In addition, the extrauterine environment is hyperoxic, which leads to a reduction in the production of growth factors (VEGF and EPO – erythropoietin) and to a cessation of growth to obliteration of the terminal capillaries of the retina – ROP phase I. The periphery of the retina remains avascular, ischemic. As a consequence of maturation of the retina and increased metabolic activity, physiological hypoxia of the retina is intensified, which causes excessive formation of VEGF and early retinal neovascularization –ROP phase II (20). Retinopathy of prematurity, similarly to other ocular disorders with pathological neovascularization, has two fundamental phases. Phase I (22nd-30th week of gestation) with relative hyperoxia of the extrauterine environment, causing a decline of the level of VEGF and vascular obliteration. Phase II (31st-44th week of gestation) is a phase with relative hypoxia, which leads to an increase in the level of VEGF and to subsequent neovascularization of the retina (6).

Classification of ROP

In 1984 an international group of paediatric ophthalmologists established the International Classification of Retinopathy of Prematurity (ICROP), which incorporated the following main parameters: scope, localisation, stage and presence of plus form of the disease (23). The classification facilitated advancement of large clinical multicenter trials focusing on the treatment of ROP (CRYO-ROP, STOP-ROP, LIGHT-ROP…). In 1987 the classification was completed with the concept of aggressive posterior forms of ROP, a description of pre-plus form of the disease and a description of practical aids in estimating the scope of zone I (24); the later study ETROP – Early Treatment for Retinopathy (4) extended the classification for the high-risk type 1 ROP and type 2 ROP (12).

Localisation of pathological changes

For determination of the localisation of changes, the retina is divided into 3 concentric zones, in the middle of which the disc of the optic nerve (OD) is located (in which the process of vascularisation takes place from the OD in the direction

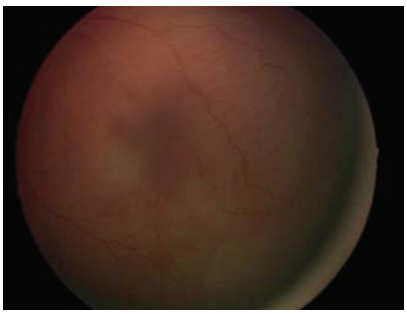

Fig. 2 ROP stage 1 – demarcation line and avascular zone.

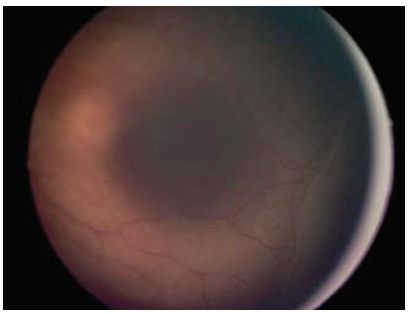

Fig. 3 ROP stage 2 – ridge between vascularised and avascular part of retina.

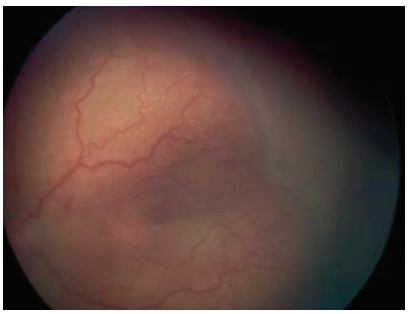

Fig. 4 ROP stage 3 – ridge with pronounced extraretinal fibrovascular proliferations with tortuosity and dilatation of capillaries – plus stage.

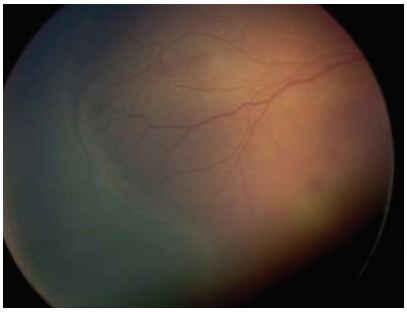

Fig. 5 ROP stage 4a – incipient partial extrafoveal amotio.

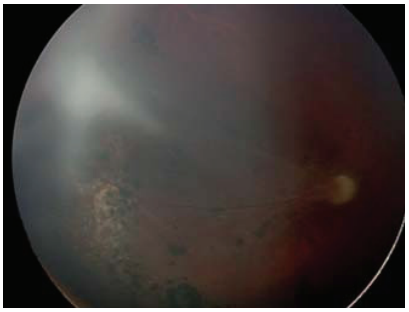

Fig. 6 ROP stage 4b – partial amotio involving fovea (patient after DLK therapy)

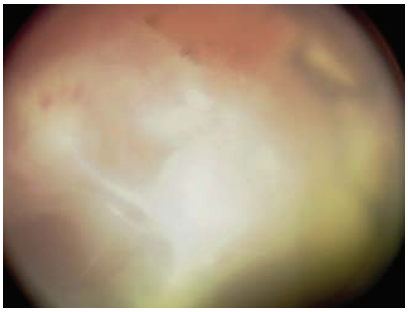

Fig. 7 ROP stage 5 – stage of total amotio retinae (patient after DLK therapy).

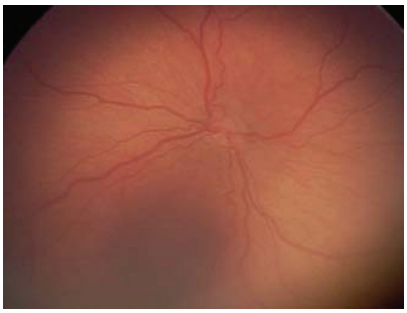

Fig. 8 ROP plus form – pronounced dilatation of veins and tortuosity of arterioles

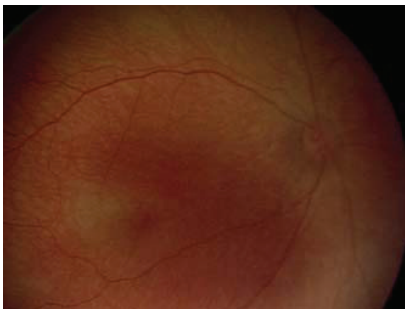

Fig. 9 ROP pre-plus form – present pronounced dilatation of veins and tortuosity of arterioles as usual.

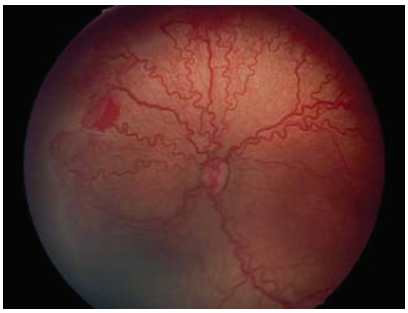

Fig. 10 ROP – posterior form AP-ROP, pronounced plus stage, neovascularization, haemorrhage.

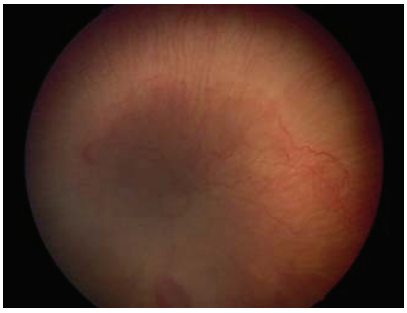

Fig. 11 ROP – posterior form AP-ROP, pre-plus stage (fuller capillaries, ending in zone I, flat neovascularization, haemorrhage).

towards the ora serrata) (Fig. 1).

Zone I – posterior pole or innermost zone – consisting of a ring, with the centre in the OD and the radius equal to double the distance of the OD – macula. This region contains the most severe forms of retinopathy from the perspective of the risk of loss of sight.

Zone II – reaches from the end of zone I nasally to the ora serrata and temporally to the equator. In practice this is sometimes divided into the central and posterior part, which is adjacent to zone I and where retinopathy is still very high risk, and the peripheral part.

Zone III – occupies the temporally remaining, half-moon area of the retina, from the equator to the ora serrata.

In clinical practice it may be problematic to determine the precise boundaries of the individual zones; therefore a practical aid was proposed in the review of the classification: with use of a 25-D or 28-D lens in examination by indirect ophthalmoscope, if the nasal edge of the lens is located adjacent to the nasal edge of the disc of the optic nerve, the temporal edge of the observed retina will be the temporal boundary of zone I. Each ROP which afflicts the retina in a continuous circle comes within zone I or II. If the examiner is not sure whether the capillaries reach to the ora serrata nasally and whether ROP is present here, it is necessary to consider the finding on the retina rather a localised finding in zone II instead of zone III.

Extent of pathological changes

The extent of the pathological changes in the individual zones on the retina is determined according to the number on the clock face (Fig. 1).

Stages of disease
In addition to the extent and localisation of the disorder, the international classification also evaluates the degree of abnormal vascular reaction on the interface of the vascular and avascular zone, in which the disease is divided into 5 stages. Before the development of ROP in a premature infant, vascularisation of the retina is not completed, this concerns an immature fundus. As more than one stage of retinopathy may occur in one eye, the stage of ROP in the eye as a whole is determined by the most severe stage of the disease which is present in the given eye.

Typical development of ROP
In its classic course, retinopathy of prematurity occurs in five continuously linked, relatively slowly developing stages.

Stage 1 – demarcation line
This is characterised by a thin, whitish-yellow line, which is relatively flat, lying on the level of the retina, forming a border between the central vascular and peripheral avascular area (Fig. 2). Slight vascular changes and irregularities of the course and dilatation of capillaries are also described, but these changes are not sufficient for determination of a diagnosis of ROP.

Stage 2 - ridge
An elevated ridge forms from the demarcation line which grows in width and height, increases in volume and projects above the level of the retina (Fig. 3). The ridge or crista is of white to pinkish colour, with low elevation. Isolated clusters of neovascular tissue may be present on the surface.

Stage 3 – ridge with extraretinal fibrovascular proliferation
In this stage, proliferation of extraretinal fibrovascular tissue occurs on the ridge, with neovascularization in the direction towards the vitreous area (Fig. 4). Fine intravitreal traction membranes begin to form. The stage is generally divided into 3 subgroups according to the extent of the extraretinal fibroproliferations infiltrating the vitreous body – mild, moderate and severe.

Stage 4 – subtotal retinal detachment
Subtotal (partial) detachment of the retina occurs in the place where the fibrovascular tissue adheres to the vascularised retina, through further proliferation the tissue grows in the direction towards the lens, with subsequent traction and contraction of the membranes. According to the localisation of retinal detachment, if the area of the macula is affected, the stage is divided into:
- Stage 4a – partial extrafoveal detachment (Fig. 5)
- Stage 4b – partial detachment involving the fovea (Fig. 6)

Stage 5 – total retinal detachment
In this stage total detachment of the retina occurs, which is most frequently of the traction type, only in isolated cases exudative type may occur. Detachment is generally in the shape of a cone, which may be open forwards or backwards, or of constricted shape (Fig. 7). Behind the lens the fibrovascular tunnel forms a stiff retrolental membrane, according to which the disease was termed retrolental fibroplasia in the past by Terry. Despite changes in the posterior segment in this stage, the shallowing of the anterior chamber later takes place, with a forward shift of the lens and the entire diaphragm. Atrophy of the iris begins, and secondary glaucoma may develop (mostly transitory), and later atrophy of the entire bulb.

Plus form of disease
Together with the indication of the stage of ROP according to the international classification, the condition of the capillaries, which is an indication of the activity and severity of the disease, is always assessed. In the case of dilatation of the retinal veins and tortuosity of the arterioles this concerns the “plus” form of the disease and the indication plus is added to the stage in question (Fig. 8). At the same time there may be a presence of rubeosis iridis, constricted dilatation of the pupil (pupillary rigidity) and reduced transparency of the vitreous body. The multicenter clinical trial CRYO-ROP Cryo therapy for ROP (3), ETROP Early Treatment for ROP (4), STOP-ROP Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (25), LIGHT-ROP Light reduction in retinopathy of prematurity (13) later defined the standard photography with a minimum amount of vascular tortuosity and dilatation, which is necessary for determining the diagnosis of the plus form of ROP, in which dilatation and tortuosity must be present at least in 2 quadrants of the eye.

Pre-plus form of disease
According to the International Committee for the Classification for ROP (12), pre-plus form of ROP, which represents vascular abnormalities of the posterior pole that do not yet reach the state of plus form, but in which dilatation of veins and tortuosity of arterioles is more pronounced than in the physiological condition (Fig. 9), was later determined for the assessment of the condition of capillaries on the posterior pole. Pre-plus form may later progress into the plus form. Capillaries may thus be present on the posterior pole without plus form, in pre-plus and in plus form.

Atypical forms of AP-ROP (Aggressive posterior ROP)
In addition to the classic course of retinopathy of prematurity with a smooth and gradual development of the individual stages, there also occurs an atypical course, known as AP-ROP aggressive posterior ROP (formerly termed rush form). This is a very rapidly progressing, severe form of ROP, primarily in very premature infants with a complicated perinatal period, with a presence of further risk factors. A characteristic feature of this form is its localisation on the posterior pole, in zone I, or in the posterior part of zone II (central part of zone, adjacent to zone I), with pronounced dilatation and tortuosity of capillaries, always afflicting all 4 quadrants of the retina (Fig. 10). The form may have a very rapid course, without the typical gradual, continuous development, in which there is no clear demarcation line and no ridge is formed. On the posterior pole there is generally a presence of a flat network of neovascularizations on the interface of the vascular and avascular retina, which progressively coarsens, elevates and forms a brush-like neovascular network, and haemorrhages may also be present. The arterioles and venulas can barely be differentiated. A lingulately-bulging avascular fold may be present from the temporal side of the retina, in the direction of the macular area. AP-ROP progresses very quickly over the course of a few days into the stage of a traction detachment. Changes on the retina are very easy to examine even for an inexperienced ophthalmologist (Fig. 11). The guide for determining the diagnosis is above all the presence of plus form of the disease with a very immature vascular bed, with short, difficult to distinguish capillaries. During the examination it is appropriate to use a 20 D lens instead of the standard 28 D (12).

Course of disease

Retinopathy of prematurity need not always progress to the 4th and 5th stages, but up to 60-80% of ROP may spontaneously cease and regress. One of the first symptoms of stabilisation of the acute phase of ROP is non-progression to the next stage (18). This primarily concerns the 1st and 2nd stages of ROP, in which spontaneous regression takes place, as well as a recession of plus form, a diminution of the ridge and a disappearance of the demarcation line, with progressive growth of capillaries into the periphery of the retina. The tendency towards spontaneous regression is characteristic primarily of retinopathies localised peripherally, in zone III and the periphery of zone II, without presence of the plus form, in infants without other risk factors and with a less complicated course of birth. In the 3rd stage of ROP the probability of spontaneous regression reaches only 50%. In severe forms of retinopathy localised in zone I, with a pronounced plus form of the disease, AP-ROP, in retinopathies beginning in the nasal part of the retina an above all in very premature infants with the presence of risk factors, the probability of spontaneous regression is negligible. In general it applies that the later the beginning of ROP, and thus the better developed the vascular system of the retina and the more peripheral the localisation of manifestations of ROP, the better the prognosis of the disease.

Regression of ROP

The active phase of ROP may leave regressive changes on the retina (termed cicatricose in the past). These involutionary changes on the retina are classified according to the International Commission for ROP:

A. Vascular and retinal changes in the periphery of the retina.
B. Vascular and retinal changes on the posterior pole of the retina.

The changes involve a wide spectrum of retinal and vascular findings: undeveloped vascularisation of the retina, abnormal branching of capillaries, straightening of temporal arcades, changes of pigmentation, attenuation of the retina, ablation of the posterior surface of the vitreous body, degenerative changes similar to grid degeneration, distortion and ectopia of the macula. Patients are later at risk of the onset of a disease of the vitreoretinal interface, in which abnormal vitreoretinal tractions may subsequently cause retinal tears, avulsion of retinal capillaries, traction or rhegmatogenous retinal detachment. The findings on the retina have an influence on the quality of vision, depending on the stage of the disease; the more severe the disease, the more severe the involutionary changes. Even if ROP does not primarily afflict the anterior segment of the eye, advanced stages of ROP have a serious impact also on its function and integrity – finding of corneal oedema, shallow anterior chamber, rigidity of the pupil, neovascularization of the iris and the occurrence of posterior synechiae of the iris with the development of cataract.

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