Chapter

Optical Coherence Tomography in Retinopathy of Prematurity

Artemiy Kokhanov, Ye He, Pooja Nikki Bisarya and Irena Tsui

Abstract

Retinopathy of prematurity (ROP) is a disease that uniquely affects prematurely born infants. This disease is caused by disordered retinal vascular proliferation and may lead to blindness. The gold standard for ROP screening, diagnosis and monitoring is indirect ophthalmoscopy examination. Optical coherence tomography (OCT) has recently been used in ROP affected infants and children in research settings. It has provided further understanding of retinal vascular development and visualization of subtle subclinical features that otherwise go undetected. In school-aged children, OCT has become an essential tool for monitoring macular sequelae of ROP such as retained inner retinal layers, epiretinal membrane, subretinal fluid, and retinoschisis. This chapter reviews the current use of OCT in infants with ROP as well as older children with history of ROP.

Keywords: cystoid macular edema, foveal avascular zone, optical coherence tomography, plus disease, prematurity, retinal detachment, retinopathy of prematurity, retinoschisis

1. Introduction

Retinopathy of prematurity (ROP) is a disorder unique to prematurely born neonates. It stems from abnormal retinal vascular proliferation which may lead to permanent damage to the retina and retinal detachment. It remains to be the main cause of childhood blindness throughout the world notwithstanding the major progress in management [1]. The first description of ROP came in 1942 by Terry [2]. At the time the condition was called retrolental fibroplasia and was thought to represent persistent fetal vasculature related to prematurity [2]. Afterwards it was determined that those findings were not innate, but rather developed postnatally in response to exogenous factors, such as exposure to oxygen [3]. Judicial use of supplemental oxygen led to reduction in incidence of ROP [4]. The advancements in neonatal care and increased survival of very low and extremely low birth weight neonates in developed countries resulted in the "second wave' of ROP [5]. The "third wave" came with the recent rapid expansion of neonatal services in developing countries where control of complications of preterm birth is lagging [6]. Each year about 32,300 prematurity survivors worldwide are impacted by permanent vision impairment due to ROP [7]. In recent years, with the increased use of OCT, there has been an ever-increasing interest in using optical coherence tomography (OCT) to comprehend ocular development as well as to detect long term macular sequelae of ROP [8]. In this chapter the utilization of OCT in infants and children with ROP will be discussed.

2. Early uses and challenges of neonatal OCT

Adoption of OCT into neonatal population has been limited due to various reasons such as absence of available equipment for quick and accurate imaging without sedation [9]. Early attempts to use OCT in neonatal population were made in operating room under general anesthesia [10, 11]. Vinekar et al. were among the first to use handheld OCT in premature infants. Using the handheld device that was made from a tabletop spectral domain OCT scanner they showed clinically undetected abnormal findings of cystoid spaces and greater foveal thickness in patients with stage 2 ROP. Also, they demonstrated the possibility of OCT imaging of unanesthetized infants at bedside [12].

3. Imaging technique

While utilization of modified unmounted tabletop OCT scanners has been reported in literature, this is challenging due to the limited portability of the device [11, 13]. Commercially available portable handheld and arm-mounted OCT systems made it feasible to obtain imaging in premature infants, but at this time they are still not widely used in clinical practice [14, 15].

The eye of a premature infant and the adult eye have many structural and optical dissimilarities. The axial length of the premature eye undergoes precipitant growth during neonatal period and then slows progressively afterwards. The cornea has steeper curvature in neonates compared to adults [15, 16]. Refractive error pattern switches from slight myopia in neonatal period towards slight hyperopia in infancy. In addition, newborn eyes have greater astigmatism [15]. If these features are not taken into consideration, difficulties, such as poor image clarity and clipping artifacts can be encountered. Thereby, imaging protocols must be configured to account for these age-specific properties [17]. OCT systems with shorter acquisition times such as spectral domain (SD) and swept source (SS) are faster making them more suitable for infants [9]. OCT angiography (OCT-A) is a rather new quick and non-invasive imaging technique to perform visualization and quantitative analysis of retinal vasculature as well as the evaluation of retinal blood flow without the need for an intravenous or intravitreal injection of a contrast agent [18–20]. This provides an alternative to fluorescein angiography. OCT-A can be used to generate various foveal vascular characteristics including vessel perfusion density, vessel length density and vascular diameter index [21]. A limitation of OCT/OCT-A is that they do not easily capture the peripheral retina where stages of ROP occur.

The imaging can be done with minimal to no discomfort to the patient. A speculum is generally needed [20, 22]. Oral sucrose may be given to comfort the patient. Arm mounted imaging systems may greatly facilitate the task as there would be no need to support the weight of the scanner. A second person would operate the software and capture the images [17, 22]. Ocular lubrication should be applied before imaging to create a stable tear film for clearer images. Scleral depression may be used to manipulate the eye position and improve peripheral views [23]. Ultimately, it has been reported that OCT imaging may even be less stressful than indirect ophthalmoscopy examinations that are routinely done to evaluate for ROP [24]. Implementation of age-specific techniques was evaluated by Maldonado et al. and it was found that the average time per imaging session decreased and there was no significant change of vital signs from baseline [15].

4. OCT findings in neonatal ROP

The standard for ROP screening has been the eye examination using an indirect ophthalmoscope. OCT allowed to visualize structures and characteristics that have been previously clinically unnoticed. Among those are preretinal tissue, epiretinal membrane, shallower foveal depression, presence of distinct inner retinal layers at the foveal center, macular edema, retinoschisis, retinal detachment, changes associated with plus disease, and optic nerve changes. Occult findings that can be visualized by OCT imaging might play a considerable role in the vision abnormalities in children with history of ROP. OCT findings have the potential to be used as an adjunct for ROP screening and monitoring. Widefield imaging using swept source OCT combined with scleral depression has the capability to visualize peripheral retinal pathology. This may have the ability to allow objective quantitative evaluation of the ROP classification. The components of ROP classification can be measured more discreetly with the use of OCT compared to indirect ophthalmoscopy [25]. In the future, it might be achievable to segment the peripheral vascular-avascular junction, create objective cutoffs for ROP stages and quantify plus disease with more objectivity using artificial intelligence derived metrics [26].

4.1 Preretinal tissue

The exact histopathologic makeup of preretinal tissue is not precisely known, but it is thought to represent remnants of hyaloidal vasculature or small isolated lumps of neovascular tissue overlying the retina [27]. These lesions also have been referred to as popcorn retinopathy [28]. It has been previously reported that the presence of popcorn retinopathy increases the risk of disease progression as well as the development of plus disease and requirement for laser photocoagulation [28]. The ability to monitor the preretinal tissue may be of importance in disease surveillance.

4.2 Epiretinal membrane

Epiretinal membrane comprises a layer of cellular proliferation on the inner surface of the retina. Epiretinal membranes are frequently seen in premature neonates [17]. Lee et al. reported that epiretinal membranes were present in 32% of cases evaluated for ROP while. They were detected by OCT imaging while not seen on indirect ophthalmoscopy examination. In nearly a third of the patients the epiretinal membrane generation foveal deformation with loss of the fovea depression [29]. The association was made between epiretinal membrane and the development of vitreous bands suggesting a tractional pathogenesis of this finding in the affected infants [20, 30]. Nonetheless, the exact clinical significance of epiretinal membrane in premature infants with ROP remains unknown, and more studies are needed to evaluate its value.

4.3 Immature retinal and choroidal morphology

Overall inner retina layer thickness at the foveal center decreases and outer retinal thickness at foveal center increases over time in the preterm period, which is driven by centrifugal and centripetal displacement of inner and outer retinal cells, respectively.

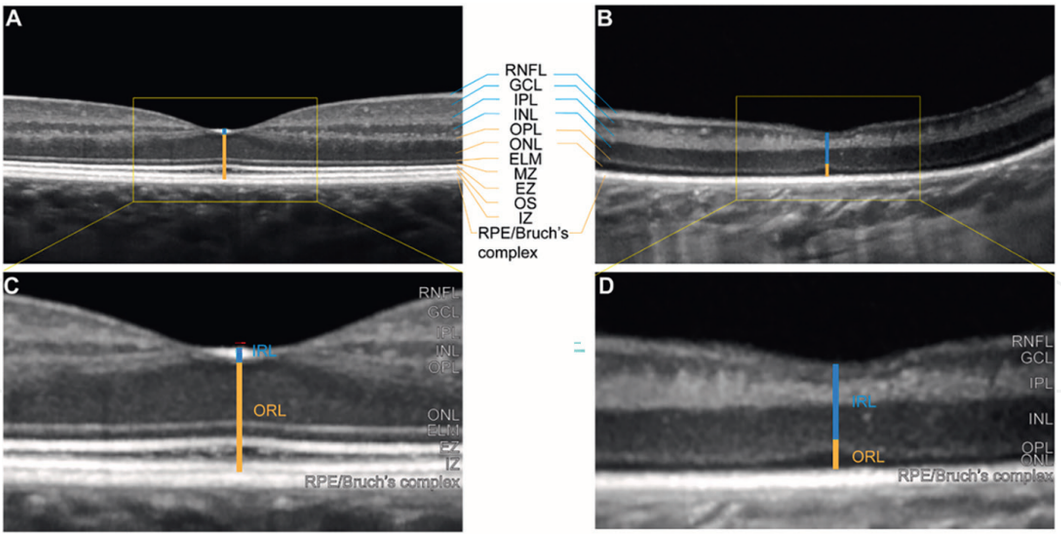

Figure 1.
Differences of foveal OCT B-scan in the healthy adult and developing retina. (A, C) Foveal OCT B-scan image from a 24-year-old adult born at term age. (B, D) Foveal OCT B-scan image from a 34-week postmenstrual age (PMA) infant (born at 25 weeks GA, birth weight 605 g). From top to bottom, the retinal layers are: Retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), external limiting membrane (ELM), myoid zone of photoreceptors (MZ), ellipsoid zone of photoreceptors (EZ), outer segments of photoreceptors (OS), interdigitation zone (IZ), and retinal pigment epithelium (RPE)/Bruch's complex. Inner retinal layers (IRL) are indicated by the blue vertical line. Outer retinal layers (ORL) are indicated by the orange vertical line. Note that the ELM, MZ, EZ, and IZ are not apparent in the immature developing retina (B, D). Adapted from [31] with permission.

It has been reported that compared to term born infant, premature infant or ROP infant eyes usually has shallower foveal pit, retain inner retinal layers at foveal center, thinner outer retinal layers, and indistinctive external limiting membrane band and ellipsoid zone (**Figure 1**) [32–34].

Choroid is another component of the eye that could be impacted in premature or ROP infancy. It has been reported that several factors including gestational age, ROP status, pulmonary status and oxygen supplementation may affect choroidal thickness [8, 22, 35, 36]. However, the impact of changes in choroidal thickness on long-term visual outcomes is still under investigation.

4.4 Retinoschisis

Retinoschisis, or abnormal splitting or retina's neurosensory layers, is not common in ROP. However, the incidence of it is not known for the most part due to the relative difficulty on indirect ophthalmoscopy or digital eye imaging systems. Some features commonly encountered in premature infants, such as corneal haze, presence of tunica vasculosa lentis or vitreous hemorrhage make particularly difficult [37].

4.5 Retinal detachment

In spite of treatment efforts, a number of prematurely born infants develop advanced ROP with retinal detachment. Accurate detection of retinal detachment is crucial in decision making process as well as in predicting future vision outcomes.

Differentiation of retinoschisis from retinal detachment and determination of foveal involvement can be a difficult task. Likewise, the decision whether to intervene may be a great challenge. OCT has been shown the ability to assess the exact location of detachment, assess the degree of retinal elevation, estimate foveal involvement and distinguish retinal detachment from retinoschisis [10, 38–40]. Shallow retinal detachments that are not seen on indirect ophthalmoscopy also can be detected earlier on OCT imaging [41]. Detecting post-laser photocoagulation exudative retinal detachment using OCT has been reported as well [42].

4.6 Plus disease

Plus disease is defined as increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels in at least two quadrants [43]. It is an important clinical sign of ROP used to identify patients that require treatment. OCT can provide further objective understanding of structural changes that occur in plus disease. Three-dimensional reconstruction of OCT images can allow visualization of vessel tortuosity not only in two dimensions, but in the third dimension across the retinal depth as well [17]. Special OCT views such as Retinal Vessel Shadow View have been proposed for evaluation of plus disease [44]. Furthermore, OCT may detect vessel elevation, a feature that is known to be related to ROP severity [45].

With the aim of reducing the impact of individual OCT features and to ensure a more comprehensive evaluation of vascular changes, a Vascular Abnormality Score on OCT (VASO) was suggested (**Table 1**). In this scoring system more uncommon features are more heavily weighted. Thus, uncommon findings have more impact on VASO score. A cut-off value of 2 was proposed. Subjects in the plus disease group had significantly higher VASO than scores in the control group. The mean difference in VASO score was larger when imaging was performed before 37 weeks corrected gestational age [45].

4.7 Macular edema

Macular edema has been a subject of recent research thanks to the ease of its detection by OCT (**Figure 2**). This is a feature that is usually not detected by traditional

Optical coherence tomography characteristics	Points
Vessel elevation	
Mild	1
Severe	2
Scalloped retinal layers	
Involving IPL	1
Involving OPL	2
Hyporeflective vessels	2
Retinal spaces	2

Table 1.
Vascular abnormality score on optical coherence tomography (VASO).

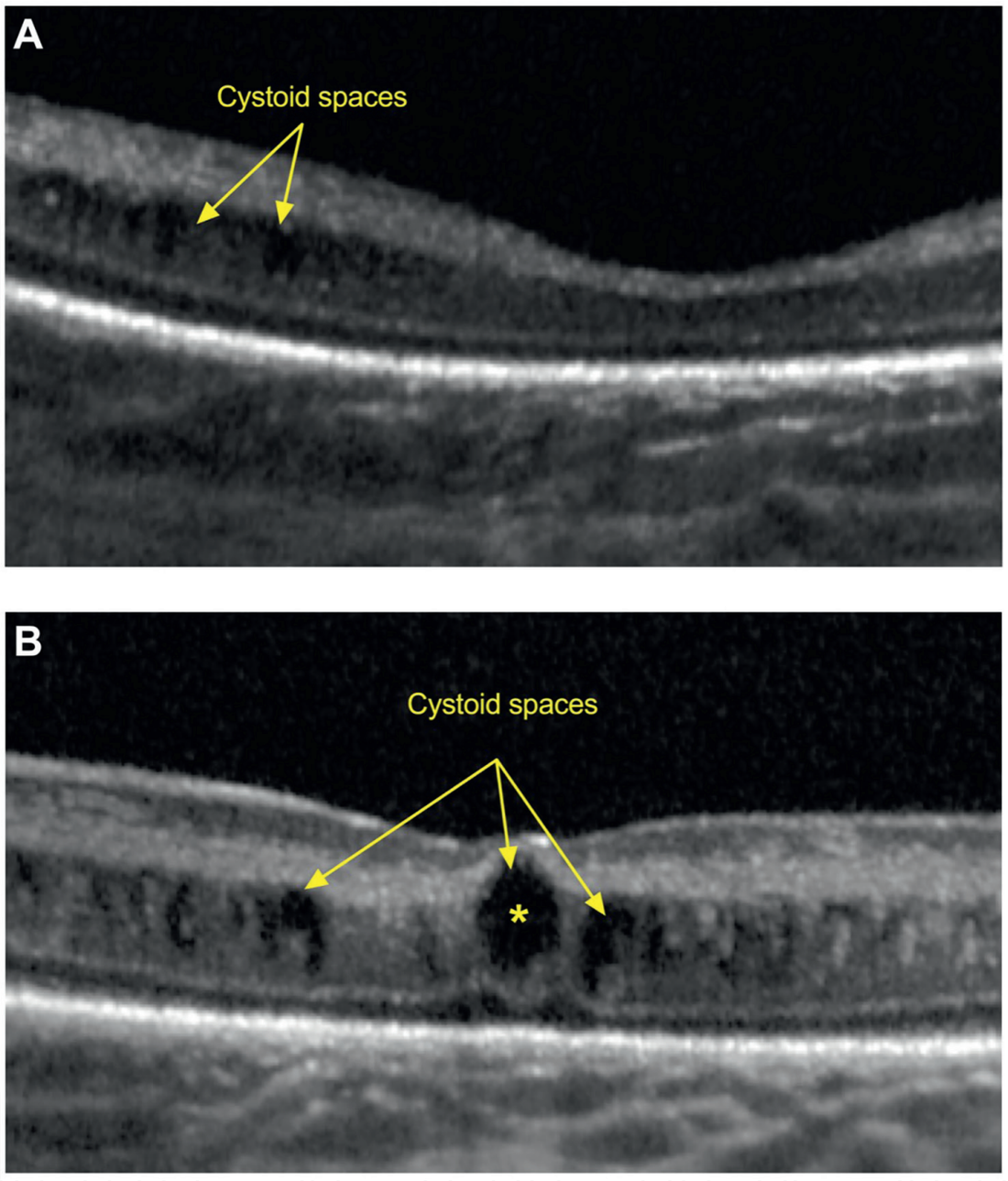

Figure 2.
Macular edema. Foveal OCT B-scan image in an eye of a preterm infant born at 28 weeks gestational age (birth weight 1220 g) imaged at 32 weeks postmenstrual age. Macular edema was only observed in the inner nuclear layer at the parafovea (A). Foveal OCT B-scan image in an eye of a preterm infant born at 25 weeks gestational age (birth weight 605 g) imaged at 42 weeks postmenstrual age. Macular edema was also only observed in the inner nuclear layer but at both fovea and parafovea (B). Yellow asterisk is located at within a cystoid space at fovea.

indirect ophthalmoscopy, and it often remains undiagnosed during infancy. Different studies use different nomenclature for this feature, which include "retinal cystoid structures" [29], "foveal/macular changes" [12], "cystoid macular changes" [46] and "macular edema of prematurity" (MEOP). This phenomenon frequently resolves spontaneously [17]. Maldonado et al. found cystoid macular edema (CME) in 50% of premature neonates imaged between 31 and 36 weeks of corrected gestational age. CME persisted in all subjects through 36 weeks of corrected gestational age. The study was not

designed for long term follow up, however the resolution of CME was observed in 9 out of 17 subjects after 37 weeks corrected gestational age [47]. Vinekar et al. performed a study on 74 patients and CME was found in 16% of patients. The resolution was reported in 100% of patients imaged at 52 weeks of corrected gestational age [12].

CME seen in premature infants is different than CME seen in adult patients. Thus, in premature infants CME is located exclusively in inner nuclear layer while in adults cystoid structures may be found in multiple retinal layers [47, 48]. Adult CME is caused by both extracellular accumulation of fluid as well as intracellular swelling of Muller cells whereas infantile CME may be represented principally by the swelling of Muller cells, or potentially extracellular fluid accumulation that is bridged by Muller cells [47, 49].

The exact etiology of CME encountered in premature infants is not precisely known. Several hypotheses have been suggested. Maldonado et al. and Vinekar et al. have proposed that CME develops as a result of the effects of neurohumoral factors, primarily vascular endothelial growth factor (VEGF). Edema may be attributed to increased vascular permeability that is caused by increased concentration of VEGF [12, 47]. This theory is plausible given the role of VEGF in the pathogenesis of ROP. Among 27 different cytokines measured in the vitreous body VEGF was found to be of the highest concentrations in patients with advanced ROP compared to controls [50]. Nevertheless, it was observed that CME might develop after intravitreal injection of bevacizumab, a VEGF inhibitor [46]. This led to a thought that other pathogenetic factors, such as mechanical traction exerted on the macula, might be involved. Tractional pathogenesis theory is also supported by an association of CME with the development of vitreous bands [30]. Furthermore, Erol et al. have suggested that lower retina pigment epithelium cell density might promote the development of CME [51].

As noted earlier, CME is a common finding in premature neonates, and its mere presence may not be necessarily associated with ROP. It may represent a non-pathologic transient stage of foveal development. Currently, there is no consensus whether the severity of CME is correlated with ROP. Dubis et al. reported in their study that severity of CME does not appear to be correlated with ROP stage [46]. However, greater severity of CME as evidenced by increased central foveal thickness, inner nuclear layer and fovea-to-parafoveal thickness ratio has been found by Maldonado et al. to be linked with higher ROP stage, presence of plus disease and the need for laser photocoagulation [47]. Similarly, Erol et al. reported that frequency and severity of CME go up with increasing ROP stage [51]. As the retinal changes have been found to correlate with gestational age and birth weight, it still continues to be unclear if those findings are due to preterm birth alone or are in connection with the effects of ROP and its management [52]. Other concomitant systemic factors may influence the development of CME. Among these factors are hypo- and hyperoxia, acidosis, arterial hypotension, presence of hemodynamically significant patent ductus arteriosus, infection, intraventricular hemorrhage, necrotizing enterocolitis, transfusion of blood products and apnea of prematurity [46]. However, Maldonado et al. made an attempt to correlate some of these factors (specifically Apgar scores at 1 and 5 minutes of life, PDA ligation, culture-proven sepsis, surgical necrotizing enterocolitis, presence of intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and hydrocephalus) with CME and could not establish the association [47].

Anwar et al. reported in their study a correlation between foveal width and retinopathy of prematurity. The foveal width was increasing in the ROP group and decreasing in the non-ROP group. This difference of trajectory was found to be independent of gestational age and birth weight – variables that are certainly concurrent with the extent of prematurity. This difference was more apparent particularly at earlier corrected

gestational age. This phenomenon has the potential to be of utility when differentiating between premature infants that need further ROP screening from those that do not. Also, it has the potential to be used as a predictor of ROP that requires treatment [53].

Another possible association that might be of interest is the correlation of CME with neurodevelopmental outcomes in prematurely born children. Rothman et al. studied neurodevelopmental outcomes in 53 very preterm infants at 18 to 24 corrected gestational age. Infants who had CME detected during routine ROP screening eye examinations were found to have poorer language and motor skills on Bayley Scales for Infant and Toddler development when compared to the infants who did not have CME [54]. Thereby, detection and evaluation of CME using OCT imaging have the potential to serve as the predictor of neurodevelopmental outcomes in prematurely born infants.

4.8 Optic nerve changes

Previously, the understanding of optic nerve development originated from different histopathology experiments [55]. The appearance of OCT has allowed for in-vivo studies of the optic nerve in humans. OCT has been used broadly for optic nerve evaluation in adults, however the use of it for infant optic nerve assessment has been limited until now. Preterm infants who underwent ROP screening were found to have larger vertical cup diameter and cup-to-disc ratio than their term counterparts in a pilot study of 44 preterm and 52 term infants. These parameters were found to have a weak association with neurologic pathology such as periventricular leukomalacia, and lower cognitive Bayley scores [56]. However, future larger prospective studies are needed before definite conclusions can be made.

5. OCT in children with history of ROP

OCT has been studied for assessment of premature children beyond the neonatal period and infancy as well. The impact of prematurity itself, ROP and ROP treatment have been studied. Features that were observed during infancy also persist in childhood and throughout adolescence, these include shallow foveal pit (**Figures 3**–**5**),

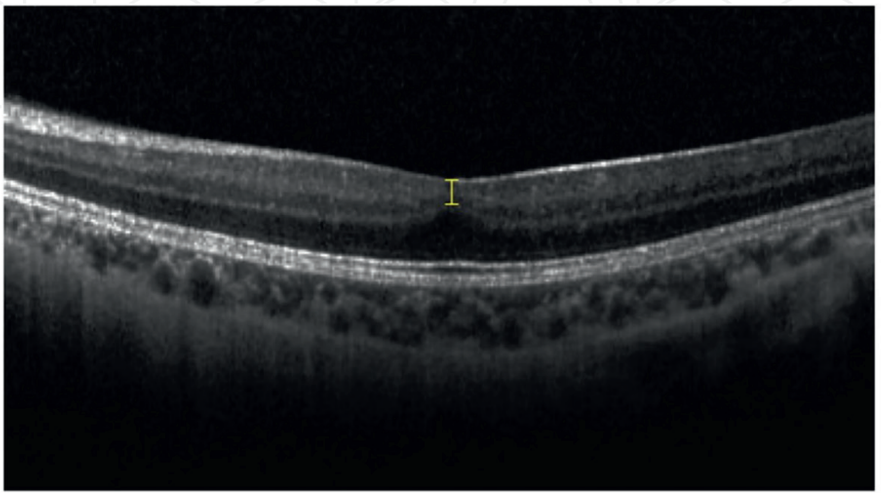

Figure 3.
Abnormal foveal contour in a premature-born child. Foveal OCT B-scan in an eye of a 12 years old premature-born child with shallow foveal pit and retain inner retinal layers at foveal center (yellow vertical line).

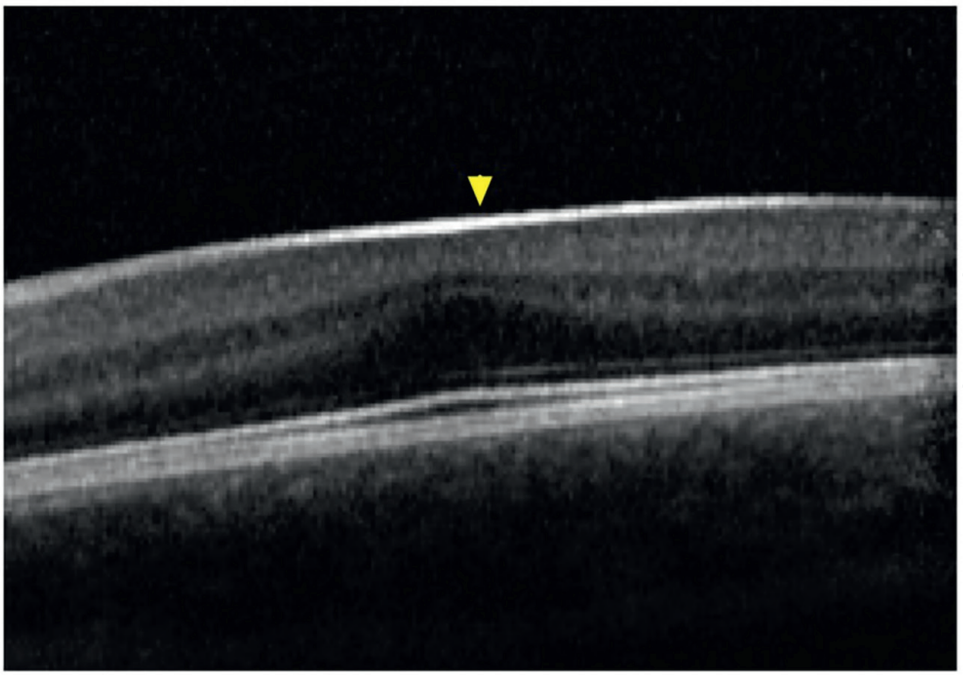

Figure 4.
Epiretinal membrane (ERM). Foveal OCT cross-sectional B-scan in an eye of a 10 years old premature-born child. ERM is presented as hyperreflective layer (yellow arrowhead) overlaying on the retina.

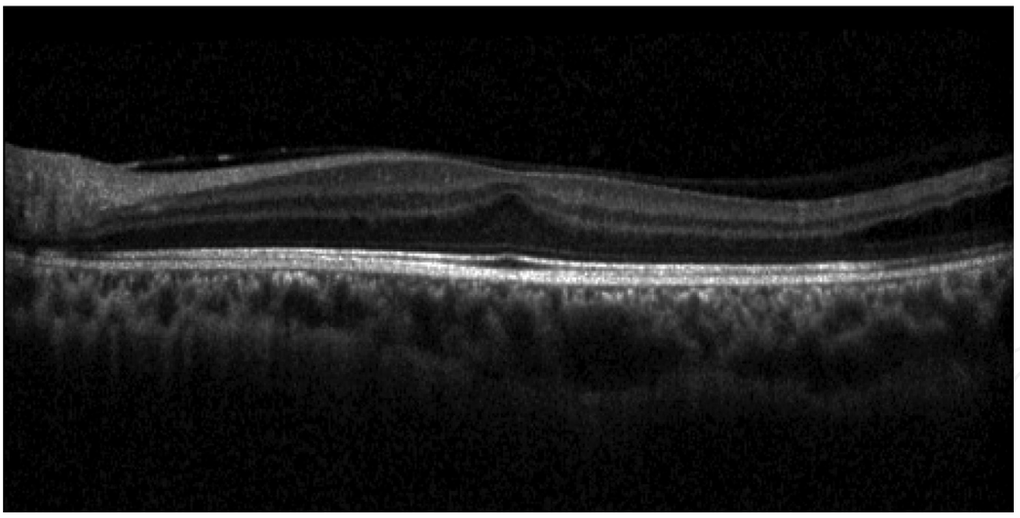

Figure 5.
OCT images demonstrating examples of retinoschisis. OCT B-scan image of temporal retinoschisis in a 17-year-old with history of ROP without treatment. Note the macular anomalies including blunting or shallow of the foveal depression and the presence of the inner retina at the foveal center.

remain inner retinal layers at foveal center (**Figures 3**–**5**), ERM (**Figure 4**), retinoschisis (**Figure 5**), and Optic nerve changes (**Figure 6**).

OCT findings demonstrated that total thickness of the retina is increased in premature children with and without ROP compared with their term counterparts [57, 58]. Tariq et al. reported increased thickness of the central macula and thinning of the outer macula in prematurely born teenagers when compared to those born at term [59].

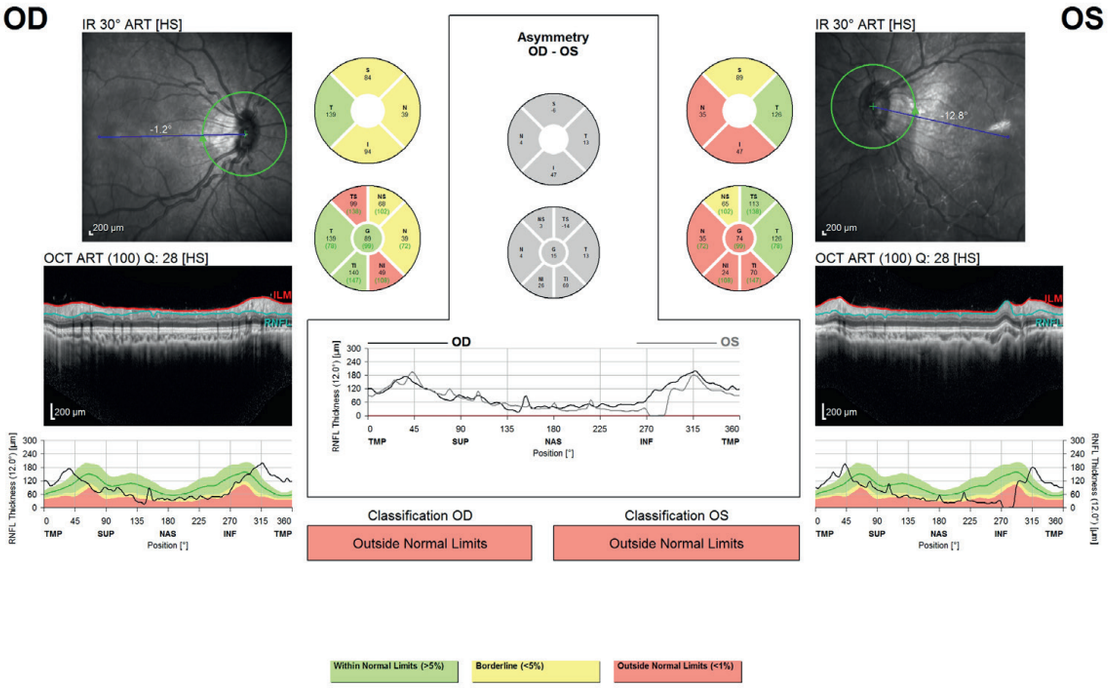

Figure 6.
Optic nerve atrophy.

Foveal avascular zone (FAZ) is a landmark that has been studied broadly in the recent years. It was found to be remarkably reduced or absent in children children with a history of prematurity with or without ROP [57, 60]. Smaller avascular zone presumably denotes arrest of normal development of retinal neurovasculature induced by premature birth [21, 61]. Positive correlation has been described between FAZ and gestational age and birth weight [62]. At the same time, FAZ was found to be smaller in children with history of treated ROP compared with those with history of spontaneously regressed ROP [21, 57]. However, the former group of patients had lower gestational age and birth weight. As such, the described differences in FAZ might be induced by more significantly immature vasculature at the time of birth [57]. Regarding vessel density, studies have reported that children with a history of prematurity have higher vessel density at the fovea when compared to healthy children [63–65], while other studies did not reveal a difference in vessel density [21, 66, 67].

Children that were born prematurely have been shown to have significantly smaller choroidal thickness 3.0 mm temporal to the fovea than children born at term. Though, choroidal thickness in other locations did not significantly differ. ROP stage had marginally significant inverse correlation with choroidal thickness 3.0 mm temporal to the fovea [68].

Children who were subject to laser treatment of ROP have been shown to have significantly narrower anterior chamber angle (ACA) compared to prematurely born children not treated with laser. In its turn, the ACA was correlated with the degree of myopia. Given the lack of statistically significant difference between ACA in preterm controls versus term controls, it can be assumed that laser treatment and not gestational age contributes to the narrow ACA [60].

Another finding reported in children with history of ROP is increased disc-to-fovea ratio, which can be detected by OCT. This finding may be caused by foveal

dragging which in turn is a consequence of cicatricial ROP. However, this association needs to be evaluated further in studies with larger cohorts [69].

6. Conclusion

OCT has been an important tool used for diagnosis and management of various ophthalmic conditions in adults and older children. Its use in neonates and infants has been limited to research. OCT has demonstrated its utility in expanding and supplying the new knowledge of infant ocular morphology and providing new insights into the pathophysiology of ROP. Also, it has provided the new outlook for retinal vascular development and allowed for a three-dimensional view of pathological ROP findings. In addition, OCT has allowed for visualization of subclinical findings that are not evident on conventional clinical examination. Thereby, OCT has the potential to become an indispensable addition to conventional binocular indirect ophthalmoscopy screening for ROP. It is feasible that OCT will aid in early identification of ROP that is at higher risk of poor outcomes and allow for timely intervention. Currently, many morphologic features detected by OCT are being studied as possible prognostic indicators in ROP. Moreover, OCT might give us new measurable treatment assessment points.

Conflict of interest

The authors declare no conflict of interest.

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