Pediatric Optical Coherence Tomography in Clinical Practice—Recent Progress

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PURPOSE. Optical coherence tomography (OCT) has revolutionized the diagnosis and treatment of adult retinal and optic nerve disease. Children were deprived of this technology until the recent development of handheld spectral-domain OCT (HH-SDOCT). In this article, we review the applications of OCT imaging in pediatric ophthalmology.

METHODS. This study was a review of the literature.

RESULTS. The acquisition and interpretation of pediatric tomograms differ significantly from those for adults, with adjustments needed to account for the shorter axial lengths, higher refractive errors, and ongoing retinal and optic nerve development in the pediatric eye. Handheld SDOCT is increasing being used as an adjunctive diagnostic tool in retinopathy of prematurity (ROP) and nonaccidental injury (NAI) by providing additional morphologic information that is not normally clinically discernible. The role of HH-SDOCT in streamlining diagnosis in infantile nystagmus syndrome, retinal dystrophies, and degenerations has been established. Optical coherence tomography can also help differentiate between pediatric intraocular tumors, for example, hamartomas and retinoblastoma; monitor tumor progression; and monitor treatment response. In addition, HH-SDOCT is establishing its role as a noninvasive monitoring tool in children affected by optic nerve pathology such as glaucoma, optic nerve atrophy and hypoplasia, optic pathway glioma, and pseudotumor cerebri.

CONCLUSIONS. Handheld SDOCT can provide novel insights into the natural history of retinal and optic nerve diseases in young children. For example, in achromatopsia and albinism, in vivo OCT studies have provided evidence of altered but ongoing retinal development in early childhood, which suggests that potentially targeting treatment at an earlier age may optimize visual function by normalizing retinal development.

Keywords: optical coherence tomography, retinal development, children’s vision

Challenges and Peculiarities of Pediatric OCT Imaging

The biometric properties of the infant human eye are significantly different in comparison to those of adults, with shorter axial lengths, steeper corneal curvatures, and greater astigmatism and refractive errors.4 Preterm infants are predominantly myopic, the degree of which decreases with increasing age until there is a shift to hyperopia by approximately 40 to 52 weeks.13,14 Age-specific adjustments in the OCT imaging protocol need to be established in order to ensure optimal image acquisition in young children. Normally, an OCT scan of the retina is obtained by pivoting the OCT beam in the iris plane. In the shorter infant eye, the OCT scanning pivot position is anterior to the iris plane, resulting in clipping of the peripheral portion of the image by the iris.4 The shorter axial length may be corrected for by shortening the OCT reference arm position such that the pivot point is positioned in the iris plane.6 The image is further optimized by adjusting the focus of the handheld probe (range, −10 to +12 diopters) to correct for any refractive errors.4 In addition, the shorter axial length of the infant human eye results in a magnified retinal image, which alters the scan position on the retina relative to an eye with a...
longer axial length. In order to facilitate comparisons at specific locations across different age groups, the lateral scales for the OCT data need to be adjusted based on age-specific axial length estimates.

Images obtained using the handheld probe may also contain movement artifacts caused by the examiner and/or the child. Therefore, HH-SDOCT imaging is limited by its lack of automatic registration for serial measurements, and it may be prudent to consider conventional table-based SDOCT imaging in older children who are sufficiently cooperative. The importance of a child-friendly environment in maximizing cooperation from infants and young children undergoing HH-SDOCT imaging should not be underestimated. Children are much more at ease in a private, spacious, and imaginatively decorated environment that is easy to navigate and in which there is control over noise and lighting. Access to information and communications technology is also suggested. In our experience, we have found that a variety of techniques can be used in order to keep children calm and cooperative for OCT examination. Optical coherence tomography scanning of young infants was most often successful if acquired when the child was seated on a parent’s lap while bottle feeding or breastfeeding. Optical coherence tomography imaging could also be successfully carried out with an infant lying supine in his or her own pram or stroller, particularly if infants were drowsy at the time of imaging. Less than 10% of children younger than 12 months of age were imaged lying supine. Children older than 12 months of age responded well to animated fixation targets, for example, age-appropriate cartoons that were employed using a portable laptop computer, which was positioned behind the examiner (Fig. 1A).

**CONSIDERATIONS WHEN INTERPRETING PEDIATRIC OCT IMAGING**

The bands identified on OCT imaging obtained at different ages ranging from 30 weeks gestational age (GA) to 65 years have been correlated with major histologic findings obtained from a range of eyes aged between 22 weeks GA to 72 years, validating OCT as a reliable quantitative tool in assessing foveal morphology (Fig. 1B). In addition, it is important to consider the corrected age of the child when assessing foveal morphology on OCT, as there are age-related variations in both the appearances and measurements of each retinal layer due to ongoing foveal development.

Normal foveal development continues until early adolescence and is associated with unique developmental trajectories.
for each individual retinal layer (Fig. 2).\textsuperscript{21} It is a complex process, involving centrifugal migration of the inner retinal layers (IRLs), retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), and outer plexiform layer (OPL) away from the central fovea, as well as centripetal migration of the cone photoreceptors into the central fovea and elongation of the outer retinal layers (ORLs), outer nuclear layer (ONL), and photoreceptor inner (IS) and outer (OS) segments with increasing age (Fig. 2).\textsuperscript{5,20–22}

As a consequence, some of the bands that are normally visualized on adult tomograms, including the ellipsoid band of the photoreceptor inner segments (ISE), external limiting membrane (ELM), and interdigitation zone (IZ), are often absent on tomograms taken from premature and younger term infants (Fig. 1B).\textsuperscript{5,20,21} There is variability in the timing of when the ISE, OS, and IZ bands all become visible in the central fovea on OCT imaging.\textsuperscript{5,20,21,23} In general, the IZ band is the last band to mature and is almost never visualized prior to 46 to 47 weeks GA.\textsuperscript{5,20,21} Pediatric normative reference data for each retinal layer band have been reported for children aged between birth and 17 years of age, which may help in the diagnosis and monitoring of pediatric retinal disease.\textsuperscript{21,24–26}

Similarly, interpretation of pediatric optic nerve morphology on OCT also requires consideration of GA. Significant differences in early optic nerve development and morphology have been observed in preterm infants as compared to term infants, including thinning of the superior, nasal, and inferior peripapillary RNFL and a larger vertical disc diameter (vDD) (908 vs. 700 μm) and cup-to-disc ratio (vCDR) (0.68 vs. 0.55 μm).\textsuperscript{27,28} As the optic nerve develops in preterm infants, there is an increase in the vDD and a decrease in vCDR.\textsuperscript{28} Peripapillary RNFL measurements are known to be thicker in children than in adults.\textsuperscript{29} As a result, previously established adult reference OCT data cannot be used in the diagnosis and monitoring of pediatric optic nerve disease. Normative reference RNFL data have been reported for children aged between birth and 17 years of age, which may help in the interpretation of pediatric optic nerve OCT imaging.\textsuperscript{5,20–22,35–37}

**Retinopathy of Prematurity**

Retinopathy of prematurity is one of the leading and preventable causes of childhood blindness worldwide.\textsuperscript{34} Retinopathy of prematurity is known to alter development of the central retina and is associated with high refractive errors and deficits in visual acuity and sensitivity.\textsuperscript{35–37} In children with a history ofROP there is persistence of the foveal IRLs, reduction of foveal pit depth, reduction in the diameter of the foveal avascular zone (FAZ), increase in central macular thickness (CMT) measurements, thinning of the GCL-IPL complex, delay in photoreceptor development, and thinning of the photoreceptor layers.\textsuperscript{5,38–55} Optic nerve morphology is altered in preterm children, with global decreases and segmental (temporal) increases in RNFL thickness measurements being reported.\textsuperscript{27,53,56,57} Choroidal thickness, which normally increases with age, is reduced in preterm children.\textsuperscript{45,50,58–60} Iridocorneal angle development and morphology are also affected, with evidence of a wider angle, a more convex iris configuration, and a shallower anterior chamber depth.\textsuperscript{50,61}

Handheld SDOCT may be a useful adjunct to binocular indirect ophthalmoscopy screening in ROP.\textsuperscript{62} Using HH-SDOCT, subclinical findings such as preretinal tissue (popcorn retinopathy), epiretinal membranes, cystoid macular edema (CME), retinal layer schisis, precise localization of retinal detachment, vascular abnormalities, and foveal architectural abnormalities not visible on conventional clinical examination can be identified.\textsuperscript{62–66}

A number of HH-SDOCT-based morphologic features are being investigated as potential prognostic indicators in ROP. Cystoid macular edema has been reported to be present in up to 63.5%, 57.1%, and 87.5% of eyes affected by stage 1, 2, and 3 ROP, respectively.\textsuperscript{5,13,25,51,67–69} The presence of CME is associated with higher hyperopia and poorer neurodevelopmental and visual acuity outcomes.\textsuperscript{70–72} A vascularity abnormality (VASO) score has been described that appears to be significantly higher in eyes with plus disease (Fig. 3).\textsuperscript{73} Increased central foveal, IRL, and foveal to parafoveal retinal thickness measurements are associated with a higher risk of developing plus disease or ROP stage 3 and requiring laser treatment (Fig. 4).\textsuperscript{74}

**Nonaccidental Injury or Trauma**

Handheld SDOCT is helpful in the evaluation of nonaccidental injury (NAI) by identifying previously unrecognized vitreoretinal abnormalities including posterior vitreous separation and multilayered retinoschisis.\textsuperscript{75} It has been used to guide treatment in infants with shaken baby syndrome by providing additional morphologic information.\textsuperscript{67} Using this information, decisions were made not to proceed with macular hole surgery in one infant with signs of chronic retinal changes and to perform additional epiretinal membrane (ERM) peel in a second infant, which resulted in an excellent postoperative visual outcome.

**Retinal Dystrophies, Dysplasias, and Infantile Nystagmus**

Handheld SDOCT is being used to characterize and monitor retinal dystrophies, dysplasias, and degenerations that present in early childhood, for example, foveal hypoplasia in albinism,\textsuperscript{16} disruption of photoreceptor integrity in Bardet-Biedl syndrome,\textsuperscript{76} retinal dysplasia in Walker-Warburg syndrome,\textsuperscript{77} and X-linked retinoschisis (Fig. 5).\textsuperscript{78} In particular, HH-SDOCT has been shown to be very helpful in identifying the etiology of infantile nystagmus syndrome (INS) (a heterogeneous group of disorders, for which there are multiple causes with different prognoses).\textsuperscript{16,79}

A HH-SDOCT diagnostic algorithm has been developed that streamlines the investigation of infants and young children with nystagmus.\textsuperscript{79} Through the identification of the presence or absence of typical or atypical foveal hypoplasia (presence of the normally absent IRLs at the fovea) and the presence of other abnormal morphologic features, it is possible to divide INS into four diagnostic categories—typical foveal hypoplasia, atypical foveal hypoplasia, abnormal foveal morphology, and normal foveal morphology—and focus further investigations (Fig. 6).\textsuperscript{79} In this way, conditions such as albinism and PAX6 mutations that are usually associated with typical foveal hypoplasia can be distinguished from other conditions such as achromatopsia (ACHM), which is characterized by atypical foveal hypoplasia (foveal hypoplasia associated with photoreceptor disruption and/or the presence of hyporeflective zone located between the ELM and RPE at the fovea), or retinal dystrophies, which are typically associated with abnormal lamination of the IRLs and ORLs, loss or disruption of photoreceptor integrity, and thinning of the ONL and RPE.\textsuperscript{79}

Using the HH-SDOCT to investigate in vivo retinal development in infants and young children affected by ACHM and albinism has provided some novel and important insights into the natural history of these conditions.\textsuperscript{80,81} In ACHM,
FIGURE 2. Summary of the development of each retinal layer over time. The mean thickness of each retinal layer plotted using a fourth-order polynomial fit for 261 participants aged between 8.4 and 333.9 months corrected age who were divided into 16 color-coded age groups. In this figure, the acronym GA refers to the corrected age of the participants, which was calculated by adding the gestational age (total time in utero) to the chronological age (based on birth date). All participants were born at term. Reprinted with permission from Lee H, Purohit R, Patel A, et al. In vivo foveal development using optical coherence tomography. Invest Ophtalmol Vis Sci. 2015;56:4537–4545. © 2015 Association for Research in Vision and Ophthalmology.
there is evidence that retinal development is not arrested but is ongoing, albeit at a reduced rate and magnitude in comparison to controls. This manifests as foveal hypoplasia, and reductions in ORL thickness, total retinal thickness, and parafoveal IRL, IPL, and OPL thickness measurements. Of particular note, ACHM appears to be a much more dynamic condition in infants and young children in comparison to adults, with ongoing changes in the degree of photoreceptor disruption observed on longitudinal follow-up.

Similarly, longitudinal OCT imaging studies in albinism have demonstrated that retinal development is ongoing in early childhood, although reduced in rate and magnitude in comparison to controls, resulting in foveal hypoplasia and a reduction in ORL thickness measurements. In contrast to ACHM, the CMT is significantly increased in comparison to controls. Interestingly, there is an initial decrease in CMT in early infancy in albinism as a result of ongoing regression of the IRLs from the fovea. This suggests that there is a period of retinal developmental plasticity in childhood in both ACHM and albinism. Potentially, targeting treatment to the earlier stages of these conditions may help normalize retinal development and optimize vision.

**Ocular Oncology**

Optical coherence tomography potentially has a role in differentiating between various pediatric intraocular tumors such as combined hamartoma of the retina and RPE (CHRRPE), astrocytic hamartomas, and retinoblastoma, which can be achieved through a systematic evaluation of tumor reflectivity, degree of involvement of individual retinal layers, associated vitreoretinal interface abnormalities, and the transition pattern between abnormal and normal retina.

Combined hamartoma of the retina and RPE appears as a hyperreflective mass on OCT, with thickening and disorganization of the IRLs and an overlying ERM associated with traction and retinal folds. In contrast, astrocytic hamartomas appear as a hyperreflective mass localized to the RNFL associated with optically empty spaces, focal vitreous adhesions, and a gradual transition between tumor and surrounding tissue.
normal tissue. Retinoblastoma lesions appear isodense or hyperdense on OCT, are associated with patches of calcification, and usually have an abrupt transition toward uninvolved retina, which helps to distinguish them from hamartomas (Fig. 7). The degree of retinal layer involvement is dependent on lesion size, which extends from involvement of the inner nuclear and middle retinal layers in isolation with preservation of the RNFL and ORLs (smaller tumors), to involvement of the full thickness of the retina (larger tumors). Preretinal seeds in retinoblastoma are located superficial to the retina, appear isodense and smooth, and are associated with shadowing of the underlying structures on OCT. Optical coherence tomography is also proving useful with regard to monitoring tumor progression, identifying new lesions and recurrences, monitoring treatment response, and guiding further management.

**Optic Nerve Pathology**

Optical coherence tomography is beginning to establish itself as a diagnostic and monitoring tool with regard to pediatric optic nerve pathology, including conditions such as: glaucoma, optic nerve atrophy, optic nerve hypoplasia, optic pathway glioma, pseudotumor cerebri and optic nerve pits (Fig. 8). It can distinguish between glaucomatous and nonglaucomatous optic atrophy in children, with INL cysts, CME, outer retinal and photoreceptor loss, total retinal atrophy, pigment epithelial detachment with associated subretinal fluid, choroidal folds, and ISE disruption more likely to be present in the latter. Optical coherence tomography may potentially serve as a noninvasive monitoring tool in pediatric glaucoma with evidence that RNFL and macular thickness measurements decrease with increasing grade of glaucomatous damage.

In primary congenital and juvenile open-angle glaucoma, OCT is being used to investigate RNFL thickness and cupping reversal in response to surgical intervention and is providing novel insights into the natural history of pediatric glaucoma. Although cupping reversal has generally been considered a marker of successful treatment outcome, recent work suggests that this may not be the case and that the preoperative cupping observed in pediatric glaucoma reflects true RNFL damage rather than a change in optic nerve compliance. Interestingly, the preoperative optic nerve head cup-to-disc ratio (CDR) may be a better predictor of postoperative RNFL thickness.

Handheld SDOCT has also been used to investigate optic nerve and retinal morphology in children with optic nerve hypoplasia. In addition to significantly smaller discs, horizontal cup diameters, and cup depths, some interesting and novel alterations in macular morphology have been characterized, including foveal hypoplasia and thinning of the RNFL, GCL, IPL, ONL, and IS.

Optical coherence tomography also can detect RNFL loss from optic atrophy occurring secondary to optic pathway glioma in older children affected by neurofibromatosis type 1. In addition, the potential of the HH-SDOCT to monitor progressive optic neuropathies such as optic nerve glioma in infants and young children unable to cooperate with traditional OCT testing devices has been established. It has been demonstrated that measurements of the RNFL, GCL, and IPL...
thickness can discriminate between children with and without vision loss from their optic nerve pathway gliomas, thus suggesting that HH-SDOCT can be used as a surrogate marker of visual function in infants and young children.96,98 Similarly, OCT can be used to diagnose and monitor pediatric pseudotumor cerebri and is potentially useful as a visual prognostic tool in this condition.99,100 An increased central macular, temporal, and superior RNFL thickness has been described in children affected by pseudotumor cerebri.101 The presence of optic atrophy and photoreceptor loss on OCT in pseudotumor cerebri are findings that are highly associated with irreversible visual loss.100 Interestingly, optic nerve parameters may also be predictive of central nervous system development and pathology, with larger vCDR being associated with lower Bayley Scales of Infant Development scores.28,33 A weak association has been described between a larger vertical cup diameter (vCD) and vCDR with periventricular leukomalacia, and a shallower cup with posthemorrhagic hydrocephalus.

DISCUSSION AND CONCLUSIONS
Pediatric OCT imaging is a rapidly expanding area that is revolutionizing the diagnosis and management of pediatric retinal and optic nerve diseases. The interpretation of pediatric OCT is a complex art, as one is often observing the effects of disease in the setting of ongoing retinal and optic nerve development in young children. The provision of normative developmental OCT data will help facilitate age-specific interpretation of pediatric OCT imaging.

Optical coherence tomography has demonstrated its potential as an objective and noninvasive diagnostic and monitoring tool in infants and young children with ROP, NAI, retinal dystrophies, infantile nystagmus, ocular oncology, glaucoma, and pseudotumor cerebri. These conditions are often difficult to diagnose and manage in infants and young children due to the limited ability of this age group to cooperate with standard adult diagnostic and monitoring tools. The incorporation of pediatric OCT imaging into the clinical assessment of pediatric retinal and optic nerve diseases is providing additional information that is assisting in management decisions. For example, several OCT measures are emerging as surrogate markers of visual acuity in optic nerve glioma (RNFL, GCL, and IPL thickness) and pseudotumor cerebri (RNFL thickness). It would be interesting to investigate if these or other OCT measures of visual acuity/function can be extended to other pediatric retinal and optic nerve diseases.

One area of pediatric ophthalmology in which the application(s) of OCT has been most investigated is ROP, where it is being used as an adjunct to binocular indirect ophthalmoscopy to provide additional information to aid in the earlier diagnosis, monitoring, and treatment of ROP. The presence of CME and altered foveal architectural and optic nerve parameters has been shown to predict visual and neurodevelopmental outcomes in ROP. It would be interesting to investigate whether these parameters can be used as universal predictors of visual and neurodevelopmental outcomes in other pediatric retinal and optic nerve diseases, as well as whether integration of OCT imaging into ROP screening results in improved structural and functional outcomes for infants with ROP in the long term.

Finally, the ability to perform in vivo OCT investigation of retinal and optic nerve diseases in infants and young children...
has provided some important insights into the natural history of conditions such as achromatopsia and albinism early in life. These conditions appear much more dynamic in children than in adults, which suggests that retinal disease in early childhood is a process that results in abnormal retinal development as opposed to retinal degeneration. It would be interesting to investigate if retinal and optic nerve development are similarly affected in other conditions in order to increase our understanding of both normal and abnormal retinal and optic nerve development and identify novel therapeutic targets. Potentially,

Figure 7. RetCam and HH-SDOCT images of two medium-sized retinoblastoma tumors located at the macula (A) and superior arcade (B). The retinoblastoma tumors appear isodense on OCT and are clearly demarcated from the surrounding healthy retina. The inner retinal layers are relatively uninvolved in these images. Reprinted with permission from Rootman DB, Gonzalez E, Mallipatna A, et al. Hand-held high-resolution spectral domain optical coherence tomography in retinoblastoma: clinical and morphologic considerations. Br J Ophthalmol. 2013;97:59–65. Copyright © 2013 BMJ Publishing Group Ltd.

Figure 8. Handheld SDOCT images of bilateral optic disc pits (white arrows) in a 6-year-old child.
targeting treatments to this critical period of plasticity in children may be the key to maximizing visual function through normalizing retinal and optic nerve development.

Acknowledgments

The authors thank Anastasia Pilat, PhD, for providing optic nerve OCT images for use in Figure 8 of this review.

Supported by the Medical Research Council, London, United Kingdom, Grants MR/J004189/1 and MRC/N004566/1; Ulverscroft Foundation, Leicester, United Kingdom; and the National Eye Research Centre and Nystagmus Network United Kingdom.

Disclosure: H. Lee, None; F.A. Proudlock, None; I. Gottlob, None

References


33. Rothman AL, Sevilla MB, Mangalesh S, et al. Thinner retinal nerve fiber layer in very preterm versus term infants and...
57. Park KA, Oh SY. Retinal nerve fiber layer thickness in prematurity is correlated with stage of retinopathy of prematurity. *Eye (Lond).* 2015;9:1594–1602.


