Retinoschisis Detected With Handheld Spectral-Domain Optical Coherence Tomography in Neonates With Advanced Retinopathy of Prematurity

Rajeev H. Muni, MD, FRCSC; Radha P. Kohly, MD, FRCSC, PhD; Alexander C. Charonis, MD; Thomas C. Lee, MD

Objectives: The recent development of handheld spectral-domain optical coherence tomography (HHSD-OCT) has enabled us to obtain high-resolution retinal scans of premature infants with retinopathy of prematurity (ROP). The purpose of this study is to document HHSD-OCT findings in laser-treated neonates with progressive ROP.

Methods: This is a retrospective consecutive case series of 3 patients with progressive ROP despite laser photocoagulation. All patients were transferred from peripheral neonatal intensive care units (NICUs) to the Children's Hospital Los Angeles. All patients had a complete ocular examination, fundus photography, fluorescein angiography, and HHSD-OCT.

Results: All 3 patients had active progressive ROP despite prior laser photocoagulation. Of the 6 eyes, 1 was excluded from the study because it had an exudative retinal detachment following laser photocoagulation. Retinal detachment was not detected on clinical examination in the 5 remaining eyes, although there was vitreoretinal traction at the ridges of the 3 of the 5 eyes. The HHSD-OCT identified presumed retinoschisis in all 5 study eyes.

Conclusions: Tractional retinoschisis may be an important finding in progressive laser-treated ROP, made possible by use of the HHSD-OCT. This finding may have significant implications for how we classify and treat patients whose ROP is progressing despite laser treatment. Furthermore, the use of the HHSD-OCT can provide valuable insight into the interaction of the retina, vitreous, and ridge in patients with progressive ROP, and it allows shallow detachments and retinoschisis to be diagnosed earlier and more accurately than would otherwise be possible.


RETNOPATHY OF PREMATURITY (ROP) is a potentially blinding condition of premature and low-birthweight infants. Infants with high-risk prethreshold ROP benefit from early laser photocoagulation of the avascular retina, with lower rates of vision loss and improved anatomic outcomes.1 However, as found in the Early Treatment of Retinopathy of Prematurity Study, despite prior laser photocoagulation, 9% of infants with high-risk prethreshold disease will still have an unfavorable outcome.3 This occurs secondary to progressive fibrovascular proliferation at the junction of the vascular and avascular retina. Stage 4 ROP represents a tractional retinal detachment secondary to this fibrovascular proliferation. Although surgery can be beneficial in some cases, it is often difficult to determine the severity of early stage 4 disease. This may be partially related to the shallow nature of the detachment and the reduced prominence of the retinal pigment epithelium in premature infants, especially those of white race.

Optical coherence tomography (OCT) has revolutionized the diagnosis and management of several adult vitreoretinal diseases. The standard OCT setup requires the patient to be cooperative, while sitting upright and holding their head steady on the chin rest. As a result, the use of OCT in very young children and infants can be problematic. The recent development of the handheld spectral-domain OCT (HHSD-OCT) (3DSDOCT platform; Biopitgen, Durham, North Carolina) has enabled us to obtain high-resolution retinal scans of premature infants with ROP. Unlike other imaging systems used in children such as the RetCam (Clarity Medical Systems, Pleasanton, California), the HHSD-OCT involves a non-contact technique with the hand piece placed close to the patient’s eye. Scott et al conclude that the HHSD-OCT is a safe, noninvasive, and effective method of obtaining in vivo high-resolution information regarding retinal morphologic features in children.

Author Affiliations: Retina Institute, The Vision Center, Children’s Hospital Los Angeles, Doheny Eye Institute, University of Southern California, Los Angeles (Drs Muni and Lee); Department of Ophthalmology and Vision Sciences, University of Toronto, Hospital for Sick Children and St Michael’s Hospital, Toronto, Ontario, Canada (Drs Muni and Kohly); and the Retina Service, Athens Vision Institute, Athens, Greece (Dr Charonis).
Here we describe a consecutive case series of 3 patients with progression of their ROP despite laser photocoagulation in which high-resolution HHSD-OCT was performed. In all cases, it was unclear whether the ROP had progressed to stage 4A based on clinical examination. The HHSD-OCT demonstrated presumed retinoschisis extending posteriorly from the temporal ridge in all 3 cases. This is a previously undescribed finding during the acute phases of advanced ROP. These findings assisted us in determining whether to proceed with more aggressive treatment, including lens-sparing pars plana vitrectomy (LS-PPV) in 1 case, although the natural history of this finding is unclear, and careful observation could be an option. Based on our experience, we believe that HHSD-OCT can be a useful tool in the diagnosis and management of progressive ROP.

METHODS

This is a retrospective consecutive case series of 3 patients with progressive ROP despite laser photocoagulation. All patients were transferred from peripheral neonatal intensive care units (NICUs) to a tertiary care pediatric retina center at the Children’s Hospital Los Angeles because of progressing ROP. All patients had complete ocular examination, fundus photography, fluorescein angiography, and examination with the HHSD-OCT. Fluorescein angiography and HHSD-OCT examinations were performed in all 4 quadrants while the infants were sedated and, in some cases, paralyzed with vecuronium. After discussing the results of the clinical examination and investigations with the parents, treatment decisions were made. Data were collected in accordance with the Health Insurance Portability and Accountability Act.

RESULTS

CASE 1

Case 1 is that of a male infant born after 24 weeks of gestation with a birth weight of 630 g, delivered by a 30-year-old, gravida 2, para 1, African American mother via normal spontaneous vaginal delivery. The patient was transferred to the NICU of an outside hospital, and his course was complicated by respiratory insufficiency, intraventricular hemorrhage, anemia of prematurity, and sepsis. The infant was treated with full laser photocoagulation in both eyes for zone 2, stage 3 ROP with plus disease at another institution at 39 weeks of age. Despite treatment, the ROP continued to progress in both eyes, at which point the decision was made to transfer the patient to Childrens Hospital Los Angeles 3 weeks after treatment for further care.

On transfer, examination using anesthesia revealed persistent tunica vasculosa lentis in both eyes. Examination of the posterior segment revealed 360° of cicatrying stage 3 ROP in posterior zone 2, extending high into the vitreous with good laser treatment of the avascular retina in both eyes (Figure 1). In the left eye, there was traction at the base of the ridge associated with elevation of the retinal vessels just posterior to the ridge, with no evidence of vitreous condensation or other membranes over the retinal surface. The view in the right eye showed prominent anterior vitreous membranes extending from the ridge itself; however, there was no evidence of any vitreous membranes overlying the retina posterior to the ridge. In addition, there was no evidence on clinical examination by multiple observers of a retinal detachment. The HHSD-OCT revealed findings consistent with bilateral presumed retinoschisis most prominently noted in the region just posterior to the temporal ridge in both eyes, with extension into the macula in the left eye (Figure 2, videos 1 and 2 [http://archophthalmol.com]). Although there was no retinal detachment seen on HHSD-OCT, the decision was made to proceed with bilateral 23-gauge LS-PPV based on the retinoschisis-like findings. The patient required repeat LS-PPV 2 weeks later for postoperative vitreous hemorrhage in both eyes. Two weeks following the second operation, the patient was found to be stable, with regressing ROP in both eyes and

Figure 1. Fundus photograph of 360° of cicatricial stage 3 retinopathy of prematurity with traction at the base in the right (A) and left (B) eyes.

Figure 2. Handheld spectral-domain optical coherence tomography of the right (A) and left (B) eyes, showing bilateral peripheral retinoschisis. Retinoschisis in the left eye extends posteriorly into the macula.
no plus disease. The patient was subsequently transferred back to the NICU at a peripheral hospital and follow-up imaging was not obtainable.

CASE 2

Case 2 is a premature infant born after 24 weeks’ gestation with a birth weight of 536 g, born to a 36-year-old, Filipino, gravida 1, para 1 mother via cesarean section. The infant was transferred to the NICU and was subsequently treated for chronic lung disease, grade 2 intraventricular hemorrhages, necrotizing enterocolitis, respiratory distress syndrome, and apnea of prematurity.

The infant was followed up at an outside hospital and had laser photocoagulation at 33 weeks of age and again at 34 weeks for stage 3 ROP in zone 1 with plus disease. The patient showed progressing stage 3 ROP despite the 2 laser sessions and was transferred to our institution.

Examination at the bedside in the NICU at 35 weeks revealed moderate neovascularization of the iris in both eyes. Examination of the posterior segment revealed active stage 3 disease in zone 1 for 360° in both eyes with mild plus disease in the right eye and moderate plus disease in the left (B) eye can be seen. C. Fluorescein angiogram of the left eye with the RetCam reveals leakage from the ridge with peripheral nonperfusion both anterior and posterior to the shunt.

Figure 3. Active stage 3 retinopathy of prematurity despite laser treatment. Active (perfused) stage 3 with mild plus disease in the right (A) and moderate plus disease in the left (B) eye can be seen. C, Fluorescein angiogram of the left eye with the RetCam reveals leakage from the ridge with peripheral nonperfusion both anterior and posterior to the shunt.

Figure 4. Handheld spectral-domain optical coherence tomography shows a ridge with early tractional retinoschisis extending from the posterior aspect of ridge in the right (A) and left (B) eyes.

Figure 5. RetCam photographs 2 weeks following repeated laser treatment in the right eye (A) and intravitreal bevacizumab treatment in the left eye (B) show resolution of plus disease and regression of the stage 3 retinopathy of prematurity in both eyes.

Figure 6. Handheld spectral-domain optical coherence tomography of the right (A) and left (B) eyes performed 2 weeks following treatment shows improvement in the extent of the tractional retinoschisis.

Consent was obtained for repeated laser treatment to skip areas in the right eye and for intravitreal injection of 0.75 mg of bevacizumab in 0.1 mL of liquid suspension in the left eye. For the following 2 weeks, the ROP regressed in both eyes, with no traction and no plus disease (Figure 5), and the HHSD-OCT revealed improvement in the tractional retinoschisis (Figure 6).
CASE 3

Case 3 is a premature infant born after 27 weeks’ gestation with a birth weight of 595 g, born to a 28-year-old, African American, gravida 1, para 1 mother via cesarean section. The infant was transferred to the NICU and intubated, and was subsequently treated for apnea of prematurity, patent ductus arteriosus, and anemia. He was exposed to both conventional and high-frequency ventilation.

The infant was followed up at a peripheral hospital and had had laser photocoagulation at 40 weeks of age for stage 3 ROP in zone 2 with plus disease in both eyes. The patient subsequently developed an exudative retinal detachment in the right eye that was slowly resolving and progressive stage 3 ROP in the left eye for which the patient was transferred to our institution.

Examination at 42 weeks of age revealed a normal-appearing anterior segment with no neovascularization of the iris. Examination of the retina revealed active stage 3, zone 2 ROP with plus disease in both eyes, with an exudative detachment in the right eye (Figure 7). Fluorescein angiography was performed, which demonstrated leakage from the stage 3 neovascularization with peripheral areas of nonperfusion posterior to the stage 3 ridge. The patient had HHSD-OCT, which demonstrated subretinal fluid and exudates in the right eye and presumed retinoschisis in the left eye, although the retinoschisis was not as pronounced as in cases 1 and 2 (Figure 8; video 4). Repeated laser photocoagulation was performed in the left eye to skip areas, as well as to the ischemic area just posterior to the temporal ridge, as seen on the fluorescein angiogram. We elected to observe the right eye. The clinical appearance gradually improved and, at the follow-up examination at 50 weeks, the stage 3 neovascularization had completely regressed, with no plus disease in either eye. There was a resolution of the exudative detachment in the right eye with persistent subretinal lipid exudates involving the macula. The patient was eventually transferred back to the referring physician, and follow-up imaging was not performed.

COMMENT

Despite the widespread use of OCT in the diagnosis and management of adult vitreoretinal diseases, its application to the pediatric population has been limited owing...
to technical challenges in this age group. The HHSD-
OCT system contains a moveable imaging hand piece that is
connected via a 1.3-m flexible fiber optic cable to a cart
holding the SD-OCT system. This handheld system elim-
inates many of the technical challenges involved in imaging
the retinae of young children. Scott et al2 provide a de-
nailed discussion of the design and image processing al-
gorithms used with the HHSD-OCT and describe its use
in children with shaken baby syndrome. With appropri-
ate lateral scanning, the HHSD-OCT enables high-
resolution 2- and 3-dimensional images with resolution
better than 10 µm. However, it must be noted that ob-
taining reliable and reproducible images with the HHSD-
OCT can be technically challenging in some cases. Ob-
taining quality images requires a clear media with an infant
that is relatively still. Although in several cases we were
able to get reproducible composite images that allowed
for registration of the OCT B-scan to a specific region of
the retina, in some cases this can be challenging.

The HHSD-OCT can be a very useful tool in the early
detection of tractional changes in ROP, which in some
instances can be quite subtle. We present 3 cases in which
the patients’ ROP continued to progress despite prior la-
sor treatments. High-resolution HHSD-OCT identified pre-
sumed retinoschisis in all 3 patients (5 of 6 eyes). In all
5 eyes with presumed retinoschisis, we did not see any
evidence of preretinal membranes. In 3 of the 5 eyes there
was clinical evidence of traction at the base of the ridge
with elevation of the retinal vessels just posterior to the
ridge. In cases 1 and 2 the HHSD-OCT showed that the
separation appears to be occurring relatively deep within
the retina. In case 3, the HHSD-OCT also revealed a sepa-
rated that we believe is consistent with retinoschisis, al-
though the images are not as convincing.

We believe that this finding represents retinoschisis
rather than a condensed vitreous membrane, as the sepa-
rated appears to occur relatively deep within the retina
in 2 of the 3 patients, and there appears to be retinal tis-
sue bridging the separated layers of the retina (Figure 2B).
Nonetheless, without histological confirmation, we can-
not definitively conclude that this represents retinoschisi-
sis. Regarding the etiology of the presumed retinoschisis,
we believe that it is most likely secondary to traction from
the ridge. This is most apparent in Figure 4A in which OCT
demonstrates that the ridge is continuous with and pull-
ing on the separated layer. This hypothesis is also consis-
tent with what we know about the cicatricial nature of ad-
vanced ROP. Furthermore, at the time of surgery in case
1, it was evident that there was significant anterior-
posterior vitreous traction extending from the ridge.

The results of the OCT examinations were a contrib-
uting factor in our management decisions, as we felt that
the presence of presumed retinoschisis possibly indi-
cated the presence of vitreoretinal traction, although it
is unclear what would have occurred if the patients were
carefully observed. The decision to proceed with LS-
PPV is multifactorial and, in case 1, was partly based on
the extent of the presumed retinoschisis. However, at this
point we cannot conclude that every patient with this find-
ing on HHSD-OCT requires LS-PPV.

The use of OCT in an infant with active stage 4A ROP
was first described by Patel in 2006.3 He described a case
in which a patient diagnosed with stage 4A ROP on clini-
cal examination in fact had stage 4B ROP on OCT. He
suggested that OCT could help guide clinical decision
making for optimal timing of LS-PPV.

To our knowledge, this is the first study of presumed
tractional retinoschisis associated with active ROP. Tech-
ically, stage 4 ROP involves retinal detachment; how-
ever, we believe it is likely that some cases of stage 4A ac-
ually represent a retinoschisis, possibly due to traction from
the stage 3. Furthermore, we hypothesize that the retinos-
chisis forms because the integrity between layers within
the retina is weaker than the interaction between the retina
and the RPE in the neonate. Subsequently, when signifi-
cant tractional forces are applied to the retina, the initial
separation occurs at the site of least resistance; therefore,
retinoschisis develops. As tractional forces strengthen, full-
thickness retinal detachment ensues.

The identification in these cases of presumed retinos-
chisis as a component of advanced tractional ROP may have
significant implications for the management of progres-
sive laser-treated ROP. It is possible that more wide-
pread use of HHSD-OCT may identify retinoschisis as a
more common finding in these patients and potentially re-
sult in earlier treatment and better final functional and anato-
mical outcomes. This finding is consistent those of with
Foos et al,4 who performed histopathology on eyes with
stage 4 ROP. They found areas of intraretinal separation
at the level of the outer plexiform layer. Our OCT find-
ings in this case support the argument for acute retinos-
chisis as a potentially common finding in progressive ROP.

Despite fairly good outcomes with LS-PPV for stage 4A
ROP, Prenner et al5 found that, of the patients who ended
up with visual acuity worse than 20/80, only 17% had evi-
dence of macular distortion clinically. The same group in
a later article by Joshi et al6 hypothesized that a subclini-
cal alteration of the macular architecture present before
surgery might be responsible for the vision loss in this
group. Joshi et al obtained OCT images of 14 eyes in 9 pa-
tients with stage 4A ROP using general anesthesia in the
operating suite before LS-PPV. Patients were turned on their
side, and images were obtained using a modified OCT im-
ager positioned adjacent to the operating table. One pa-
tient in this study had repeat OCT 2 years after LS-PPV
and was found to have abnormal foveal architecture in both
eyes. Interestingly, of the 14 eyes imaged preoperatively,
1 patient had schisislike changes and another had intraret-
inal cystoid changes in the fovea.

Patients with progressive ROP may have permanent loss
of vision as a result of tractional retinoschisis, despite the
surgical release of the tractional forces. It may also explain
why many patients with a history of ROP who appear to have
normal foveal architecture clinically still have profound vi-
sual loss. Waiting for clinical evidence of stage 4 may be too
late, as patients may have already developed permanent vi-
sion loss from retinoschisis-associated damage.

In summary, tractional retinoschisis may be an impor-
tant finding in progressive laser-treated ROP made pos-
sible by the use of the HHSD-OCT. Although further OCT
studies will be required with a larger number of patients,
we believe that this finding may have significant implica-
tions for how we classify and treat patients who are pro-
gressing despite laser treatment. However, at this time, it
is unclear what the natural history of retinoschisis in ROP is, and whether early surgical intervention alters this outcome. Therefore, it should be stressed that we cannot make treatment recommendations at this point based on the HHSD-OCT findings. However, it is evident that the use of HHSD-OCT can provide valuable insight into the interaction of the retina, vitreous, and ridge in patients with progressive ROP, and it allows shallow detachments and possibly retinoschisis to be diagnosed earlier and more accurately than would otherwise be possible.

Submitted for Publication: March 29, 2009; final revision received June 2, 2009; accepted June 7, 2009.

Correspondence: Thomas C. Lee, MD, Retina Institute, The Vision Center, Childrens Hospital Los Angeles, 4650 Sunset Blvd, PO Box 27980, Mailstop 88, Los Angeles, CA 90027-0980 (tleemd@gmail.com).

Financial Disclosure: None reported.


REFERENCES


Ophthalmological Ephemera

In 1795, Dr Isaac Thompson concocted an eye water of zinc sulfate, saffron, camphor, and rose water. It was sold as late as 1939. This is 1 of a series of 32 medical trade cards advertising the product from 1875 through 1895.

Courtesy of: Daniel M. Albert, MD, MS.