Key to Retinal Assessment: Making Visible what is Invisible
Jerome Sherman

Disclosure:
Dr. Sherman has lectured and received honorarium from Carl Zeiss Meditec, Topcon, Optovue, Optos, Eye Solutions, PHK, Nove Health, ArctiOptx, Drispace, Annidis, Innova, and received support for Retina Revealed from all and also from Heidelberg and DGH.

The Diagnosis of Retinal Disease Invisible to Ophthalmoscopy
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Structure        Function

- Ophthalmoscopy
- Fundus photography
- Panoramic Imaging (Optos)
- Fluorescein Angiography
- B-scan ultrasound
- SD-OCT & OCT A
- HRT and GDx
- FAF -Fundus autofluorescence

- Visual Acuity
- Pupils
- Fields, PHP, MAIA
- Color vision
- Contrast Sensitivity
- Rabin cone contrast
- ERGs
- EOG
- pERG mf ERGs
- VEPs (pattern & flash)

BEYOND OPHTHALMOSCOPY

True or False:
If the retina looks normal with an ophthalmoscope, the retina is normal.
FALSE!

BEYOND OPHTHALMOSCOPY

Back to Basics

BEYOND OPHTHALMOSCOPY

But Why Back to Retinal Anatomy?
- Do you remember the 10 layers of the retina?
- Do you recall that the 9 neuro-sensory layers of the retina are invisible to ophthalmoscopy and only the RPE is visible?
- Have you ever said, Mrs. Jones, I am going to examine your rods and cones?
Although the retinal pigment epithelium (RPE) is only a single layer of cells, it appears as two reflective layers with a dark zone in between on high definition OCT scans. The "inner reflection" has been referred to by some authors as the outer segment-RPE interdigitation (OS/RPE) or Verhoeff's membrane. The outer reflection is the RPE/Bruch's membrane complex (RPE/BM). Note the two reflections from the RPE complex are only visible on high definition scans. On lower resolution OCT scans the RPE generally appears as one solid thick band.

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**Photoreceptor Integrity Line as Revealed by SD OCT- lulu.com**

PIL: A biomarker for rod and cone integrity

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**Invisible to Ophthalmoscopy**

- Inner Retina/Vitreous
  - NFL
  - VMT

- Middle Retina
  - Exudates (in diabetes)
  - Retinoschisis

- Outer Retina
  - Photoreceptors (PIL)
  - Early drusen
  - Early choroidal neovascularization
  - Early macula holes
Only 5% of photoreceptors in the retina are cones, and these are concentrated at the fovea. As reported by Osterberg in 1935, the density of cones drops off rapidly (but not abruptly) just several degrees from the fovea, and rods begin to predominate outside of the central 5 degrees or so. This known distribution of rods and cones is important in the interpretation of the PIL in SD OCTs. The width of the OCT section (6mm) is denoted on the Osterberg graph by the vertical dashed green lines.


When compared to a normal control, the abnormalities in the patient’s OCT scan are more obvious. Unlike the normal control where the PIL is present throughout, the patient’s PIL was absent throughout the scan except a small segment under the fovea.

Images from the right eye above and left eye below with a higher resolution Raster image. There is evidence of some cones being present, which explains why the vision is relatively good.

Patient #2 LMBB: OCT OS

Older brother
What’s missing?

Additional Clue

- Polydactyly – patient had 24 digits at birth and had 4 removed!

Diagnosis
- Probable Laurence-Moon or Bardet-Biedl or LMBB syndrome and not autism!
- Genetic testing for the BBS1 gene is now available (Carver Nonprofit Genetic Testing Lab at www.carverlab.org).
A comparison of standard fundus photos to AF images clearly reveals unmistakable abnormalities in the AF images only. Note that the small foveal AF lesions are often not round and many are fish-tailed or pisciform in shape, suggesting perhaps the fish-tail lesions in Stargardt’s Disease with fundus flavimaculatus. (link to RR #14) The symmetry of the AF findings are quite typical of inherited retinal degenerations. (See RR #54 part 1 and part 2)

Case 2(5 yo daughter): Topcon Fundus Photos OD and OS

Case 2(5 yo daughter): Above are the fundus photos of the five year old daughter. She had no symptoms and her best corrected VA was about 20/40 in each eye. The images above reveal normal white glistening reflections off the internal limiting membrane in each eye. This is an expected finding in young children. The fundus images were interpreted as essentially normal in both eyes.
Case 2 (5 yo daughter): Optomap® FAF Image OD and OS

The AF images reveal a subtle macula bulls eye in each eye. Note the hyper-AF ring around the macula in each eye. This pattern is abnormal.

Case 2 (5 yo daughter): Topcon 3D OCT OS

The ELM is abnormal in both grey scale and in color.

Case 3 (4 yo daughter): Fundus Photography

No marked abnormality is obvious in the color fundus photos or in the AF images in the 4 yo daughter.

Case 3 (4 yo daughter): Topcon 3D OCT OD

With parental consent, chocolate was used to bribe the 4 yo. Cooperation improved for the OCT images. As revealed in her 5 yo sister, the PIL is somewhat thin and the ELM is thickened, irregular and hyper-reflective here in the right eye.

5 y/o daughter OD vs Normal

Does photoreceptor degeneration result in debris accumulating on ELM?

A Novel Finding which may be a biomarker for very early degen in SD

Introducing…
The Rabin Cone Test
Early Disease Detection & Ophthalmic Health Management

Jerry Sherman, OD
**What is the Rabin Cone Test?**

- Color Vision Test Sensitive Tests 3 colors at different contrast levels
- Enough to Measure Subtle Changes in Cone Function
- Based on Clinical Research
- Fast & Easy to Administer
- Medicare Reimbursable
- Independently Validated

**Helmholtz Invented the Ophthalmoscope in the 1860’s**

- With an SD OCT, we are learning that most retinal disorders are invisible to ophthalmoscopy in the early stages but easily detected with SD OCT.
- 150 years after Helmholtz, SD OCT is rapidly relegating ophthalmoscopy to a much more modest role in diagnosis.

**A New Way of Visualizing Vessels Optovue Avanti**

- OCT-Angiography (OCTA) is a new imaging modality until now only available in research prototypes
- Identify retinal circulation using the intrinsic motion of the blood cells in the vessel
- Unlike OCT, it acquires functional rather than structural information. Usually viewed in en face projections
- Unlike angiography, it requires no contrast medium and the data is three-dimensional and depth-resolved

**Spectral-Domain (High-Speed) OCT System**

- OCT Angiography features is not available for sales in US

**En Face Visualization**

- En Face Visualization of layers based on retinal anatomy
- Not available for sale in US
Angioflow images of Normal Macula

- 3 x 2 mm, 304 x 304 pixels (superficial capillary plexus)
- 6 x 6 mm, 304 x 304 pixels (superficial capillary plexus)

Angioflow images of Normal Optic Disc

- 3 x 3 mm, 304 x 304 pixels (radial peripapillary capillary)
- 4.5 x 4.5 mm, 304 x 304 pixels (radial peripapillary capillary)

Enhanced HD Line

- 12mm EHD Line, 52 YrO Male, 20/20
  - Tracking and Y-axis zoomed

- 13mm EHD Line, 45 YrO Female, Pacific Islands, -6.5D,
  - Scanned through contact lenses. No Y-axis zoom

Dx of Optic Neuropathies: Beyond the Basics

Case 50 – GCC, VEP and RAPDx
Comparison of the right and left maculas and discs of each eye failed to reveal an explanation for her symptoms.

The GCC asymmetry is not reflected in the central threshold visual fields. Learn more about GCC – link.

The Wellness exam was performed. This test has recently been reported to have 91% sensitivity and 99% specificity [ref ARVO abstract] Although the SD OCT scans through the fovea were normal in each eye, the Ganglion Cell Complex (GCC) was observably thinner in the right eye than in the left eye. Quantitatively, a difference of greater than 10 um is clinically significant: here the right GCC is 12 um thinner than the left.

In our 29 y/o patient with blurred vision in her right eye, the VEPS are normal in amplitude but delayed in the right eye. Under high contrast conditions, the VEP P100 latency is delayed by 33 msec in the right eye when compared to the normal latency in the left eye. [Under standard Nova-DN conditions, the entire pattern reversal stimulus contains 32x32 checks.]
With the patient’s distance prescription in place (with an additional +1.00 D to compensate for the 1 meter working distance), the central 5 degrees of the visual field is focused onto the central 5 degrees of the fundus which corresponds to the macula. Action potentials are then generated by the ganglion cells which are transmitted through the visual pathway to the occipital lobe. Note that the central 5 degrees of the visual field (in orange and yellow) project onto about 50% of the occipital lobe. Hence, the VEP is a test of macula and macula projections measured at the level of the occipital lobe with surface electrodes. VEPs are often far more sensitive than visual fields to optic neuropathies affecting the papillo-macular bundle (PMB), but also in cases without any evidence of PMB compromise. Diopsys VEPs are far simpler to obtain than traditional VEPs.
The typical stimulus for a mfERG is shown in the left image above. Elements 153 hexagons pattern reverse from white to black and black to white in a pseudorandom sequence. The resultant response from the retina is topographically accurate. mfERG is a full drivers solution. The total field size often chosen is a standard 24-2 visual field (which is 54 degrees horizontal and 48 degrees vertical). The amplitude of the mfERG components are color coded to aid interpretation. The traditional color coding is employed; bright colors correspond to high amplitude areas whereas dark colors represent low amplitude zones. White and red are below normal, light green is normal and blue is reduced.

The mfERG in November 2008 still appears normal in the right eye even though the patient was now symptomatic OD with reduced VA and a disorganized PIL/junction OD. The mfERGs above are quite similar to the mfERGs under the same condition obtained 8 months earlier. In this case, the PIL/junction appears to be more sensitive to dysfunction than the mfERG.
BEYOND OPHTHALMOSCOPY

Multi-Spectral Imaging MSI

by Annidis

Retinotoxic drug damage visualization
A 25 year old female presented with blurred vision in her right eye. She was concerned about her eyes because she was told by her neurologist that patients with her disorder, neurofibromatosis type 1, sometimes develop visual problems. Previous eye exams failed to reveal any unusual findings. Our patient was first relieved when a -1.00 lens corrected her vision in her right eye to 20/20 and a -0.50 in her left eye also resulted in 20/20. The slit lamp exam revealed several iris spots which were perhaps small Lisch nodules or just commonplace iris freckles.

The fundus through a dilated pupil was considered to be unremarkable with direct ophthalmoscopy and with indirect ophthalmoscopy (with a 78D lens and with a BIO). Fundus photography was also judged to be unremarkable in both the right and left eye. SD OCTs with the Topcon 3D OCT 2000 also appeared to be within normal limits. All retinal layers, including the Photoreceptor Integrity Line (PIL) appeared normal. The normal PIL under the fovea predicts normal (corrected) visual acuity. In addition to the retina, the vitreous and the choroid also appeared normal in each eye.

The Annidis Multi-Spectral Imaging, of our patient with NF, uses 10 different LEDs, each of a different color and somewhat different penetration range. The Green, Yellow and Amber LEDs reveal detailed information about the shallow retinal structures. The Red and Infrared LEDs penetrate deeper into the retina and choroid and reveal abnormalities not visualized with the Green, Yellow and Amber LEDs.

The Annidis MSI Capturing Data

Multi-Spectral Imaging (MSI) Fundus Spectral Slices

This simplistic diagram demonstrates the different penetration depths of several LEDs and the various images that may result.
Actual data from the left eye of our patient with NF. Ten LEDs are used and the resulting images are displayed. The Color Composite is a pseudo color image and is based upon the some of the data generated by the 10 LEDs.

The Color Composite Image is a composite of the Green and Red1 Images, useful for comparing data acquired with the Annidis MSI to standard fundus photography.

Although traditional fundus photography (top left) and Optos Color Image (top right) yield some information about the deep lesions, the Annidis MSI yields important information about the deep lesions not clearly visible before.

Note similar findings in the left eye as well.

The patient has hundreds of flat, coffee colored lesions of various sizes on her body which represent melanin deposition. These are generally termed cafe-au-lait spots. A much smaller number of lesions are somewhat raised and these represent cutaneous and subcutaneous neurofibromas. Both are common in NF type 1.

Some Examples Invisible to Ophthalmoscopy

- RNFL thinning can be detected and measured with OCT (and GDx) prior to ophthalmoscopic evidence leading to the early treatment of glaucoma and other optic neuropathies.
- Vitreal retinal traction can be documented with OCT prior to ophthalmoscopic evidence.
- Macula hole documented with OCT but invisible with O scopes.
- RPE loss at the outer and inner plexiform layer, which may not be detectable with ophthalmoscopy, can easily be imaged with OCT.
- Loss of photoreceptors are now easily detected with SD OCT, and the loss may never be detected, even decades later, with ophthalmoscopy.
- Exudates in diabetic and other vascular diseases can be detected with SD OCT far earlier than with O scopes.
Spectralis® OCT OS

The vertical section through the fovea depicts vitreal macular traction, which distorts the presence of a normal foveal pit (see page 17).

Future VMT tx: Microplasmin injection
- a recombinant truncated form of human plasmin that is active
  - functions as a thrombolytic agent causing enz pharmacological induced vitreolysis
  - Nonsurgical PVD
  - The enzymatic agents alter the biochemistry of vitreous
    - Liquefaction of the vitreous occurs
    - LYSIS between vitreous cortex and ILM is the final outcome

Microplasmin (ThromboGenics)
Could it be a future tx for symptomatic VMT?
- MIVI-TRUST
  - N = 650 pts
  - Microplasmin intravitreal injection vs placebo
    - 26% of ALL tx pts had resolution of VMT
    - In looking at pts w/o ERM, 37% had resolution of VMT
    - 40% of pts with MH had a complete closure
    - Improving VA and restoring ocular structures without complications associated with PPV

Case 10: Elevations vs. Excavations
- unilateral congenital optic nerve abnormality detected five days after birth and enlarged blind spot in the left eye.
- Patient reports vision in both eyes is excellent. BCVA measured 20/15-2 OD and 20/15-1 OS.
- Fundus photo of the anomalous disc and of the macula, as well as a 6mm x 6mm scan box. The horizontal section through the macula reveals that the PIL is normal temporally, becomes mildly attenuated under the fovea and eventually disappears towards the optic nerve head. Note the optic disc excavation nasal in this scan.

For the full case study go to: Retina Revealed
Case 18 - Morning Glory Disc Coloboma
The DGH B-scan Scanmate below is a vertical slice through the optic nerve head and the retinoschisis inferior to the optic nerve head.

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BEYOND OPHTHALMOSCOPY

Ophthalmoscopy is really a gross way of evaluating the retina

- Yes, it is still the standard of care but SD OCT is rapidly becoming the standard of care.
- OCT is already the standard for retinal specialists.
- Best is both!
- With OCT, myriad disorders in numerous patients can be diagnosed years earlier than with ophthalmoscopy.
- In many disorders, earlier detection leads to better outcomes.
- Early detection of treatable diseases decreases the risk of malpractice litigation.

BEYOND OPHTHALMOSCOPY

Typical retinal vascular changes in Sickle Cell Retinopathy have been presented in detail in RR #29. See RR #29 for full details.

Optomap® Color Fundus Image of Right Eye
Optomap® Red Separation Fundus Image of Right Eye
Optomap® Green Separation Fundus Image of Right Eye
Optomap® Color Composite and Fluorescein Angiography Image Comparisons of Right Eye

Leakage from the "sea fan" is better visualized when comparing a timeline of FA images. Note the dark areas of capillary avascularity surrounding the "sea fan" at a higher magnification FA image, the growth of new vessels on the surface is more apparent than it is on the color image.

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Note the web of new vessels (red arrows) extending from the disc into the vitreous.

Rotation of the fundus image to match the orientation of the OCT section

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Invisible to Ophthalmoscopy: Plaquenil Toxicity

BEYOND OPHTHALMOSCOPY

Abnormal
Normal

Early Plaquenil Toxicity
OS
OD

BEYOND OPHTHALMOSCOPY

Invisible to Ophthalmoscopy:
RP in 10 Year Old Black Male

BEYOND OPHTHALMOSCOPY

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www.retinarevealed.com

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www.retinarevealed.com

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