HOW TO DISTINGUISH RETINAL DISORDERS FROM CAUSES OF OPTIC NERVE DYSFUNCTION?

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LEARNING OBJECTIVES

1. To define the overlapping clinical presentations of acute unilateral visual loss in a young patient that might suggest either retinopathy versus optic neuropathy

2. To describe the big red flags for retinal disease versus optic neuropathy

3. To define the key clinical findings for subtle or occult retinopathy (e.g., acute zonal occult outer retinopathy)

4. To list some specific diagnostic testing that might help with making the correct diagnosis or retinal versus optic nerve etiologies for visual loss

CME QUESTIONS

1. Which of the following ocular symptoms is most likely to be associated with an optic nerve rather than retinal etiology for visual loss?
   a. Flashing lights or photopsias
   b. Metamorphopsia (including micropsia/macropsia)
   c. Day or night blindness (i.e., hemeralopia or nyctalopia)
   d. Pain with eye movement

2. Which of the following is more likely to be a sign of optic neuropathy than retinopathy as the etiology of unexplained visual loss?
   a. Red color desaturation in the affected eye
   b. An equal inter-eye subjective light brightness test
   c. Normal Ishihara or HRR color vision testing
   d. A positive prolonged macular photostress test

3. Which of the following abnormal electrophysiologic findings would be expected to differentiate maculopathy from optic neuropathy as the etiology for visual loss?
   a. Visual evoked potential
   b. Full field electroretinogram
   c. Multifocal electroretinogram
   d. Electrooculogram

KEYWORDS

1. Optic Neuropathy
2. Retinopathy
3. Electrophysiology
4. Optical Coherence Tomography
5. Macular Photostress Test

INTRODUCTION

The clinical presentation of acute unilateral visual loss in a young patient can be due to a number of conditions including possible retinopathy or optic neuropathy. Although demyelinating optic neuritis is the most common unilateral optic neuropathy to present in a young adult to a neuro-ophthalmologist, the possibility of acute retinopathy should also be in the differential diagnosis especially when specific red flags for retinal disease are present. The overlapping clinical presentation of retinal and optic nerve disorders in this setting can be challenging and will affect the patient’s evaluation, treatment and prognosis. The main diagnostic dilemma is that a young otherwise healthy female patient who presents with acute unilateral visual loss may have idiopathic or demyelinating optic neuritis or a subtle or occult retinopathy (e.g., acute zonal occult outer retinopathy). This manuscript will describe the key differentiating clinical symptoms and signs and the specific diagnostic testing that might help with making the correct diagnosis.

ILLUSTRATIVE CASE

A 22-year-old white woman presents with a chief complaint of acute unilateral loss of vision in the right eye (OD). She had some vague flashing lights OD as well as glare but no loss of brightness or color. The left eye is asymptomatic. She has no other neurologic symptoms. There is mild pain with eye movement OD. She has a family history of multiple sclerosis (MS) in a maternal aunt but no other medical disorders run in her family. Her past medical and surgical histories were negative. Her social history was non-contributory and she did not smoke or drink alcohol. She was taking no medications and had no medical allergies. The remainder of her review of systems was negative and she specifically denied any prior neurologic signs or symptoms. She denied any metamorphopsia, micropsia, macropsia or day or night blindness (i.e., hemeralopia or nyctalopia).
On neuro-ophthalmologic examination the visual acuity was 20/25 OD and 20/20 OS. The examination of the left eye was completely normal. The pupils were isocoric and reactive OU but there was a trace right relative afferent pupillary defect (RAPD). The slit lamp biomicroscopy showed no uveitis. External, extraocular motility, and intraocular pressure exams were all normal. She correctly identified 13/14 Ishihara color plates OD and 14/14 OS. Humphrey visual field showed an enlarged blind spot (Figure 1) with some breakout superiorly and inferiorly OD but was normal OS. The fundus examination showed a normal macula, vessels, and periphery OU. There was no optic disc edema or optic atrophy. There were no vitreous cells noted. There was no peripapillary atrophy, cystoid macular edema, or epiretinal membrane formation.

She was seen by a comprehensive ophthalmologist who referred the patient to outside retina specialist who confirmed the normal retinal exam. An optical coherence tomography (OCT) of the macula and a fluorescein angiogram were both normal. A contrast cranial magnetic resonance imaging (MRI) study was negative for optic nerve enhancement and no demyelinating white matter lesions were seen. The patient was told that she might have “multiple sclerosis” and then referred to neuro-ophthalmology as “possible demyelinating optic neuritis.”

Clinical questions

1. Is this a case of retrobulbar optic neuritis?
2. Is this retinal or neuro-ophthalmic disease?
3. How can we clinically differentiate optic nerve from retinal etiologies for visual loss?
4. What diagnostic testing might be useful at this point?

Ocular symptoms that are suspicious for retinal etiology for the visual loss include flashing lights or photopsias, metamorphopsia (including micropsia/macropsia) in macular disease (e.g., epiretinal membrane), or day or night blindness (i.e., hemeralopia or nyctalopia). In contrast, some clinical features on exam that might suggest optic neuropathy over retinopathy include abnormal color testing, nerve fiber layer field defect, and optic disc edema or pallor. Red color desaturation and more severe dyschromatopsia are more common in patients with optic neuritis than in acute maculopathy. The light brightness test in this patient showed no subjective light or color desaturation in either eye and color testing was near normal by Ishihara testing. A macular photostress test might be useful in patients with central loss. In this test, the patient is shown a moderate light stimulus for 10 seconds of light exposure in each eye. The time to recovery of one line of vision over the best corrected visual acuity line is recorded. In most normal individuals the macular photostress time is less than 60 seconds of recovery time. In a patient with suspected optic neuropathy the result also would be expected to be 60 seconds or less but in macula disease it might be prolonged (e.g., more than 60–90 seconds). A formal visual field might show a ring scotoma (rather than a central or cecocentral scotoma or nerve fiber layer defect) on automated or kinetic perimetry in retinal disease (e.g., bull’s eye maculopathy). An enlarged blind spot (Figure 1) would be a very atypical presenting visual field defect (perhaps < 2%) for optic neuritis and suggests a problem with the peripapillary retina.

In most cases of retinal disease the fundus exam is diagnostic (e.g., cystoids macular edema, macular hole, epiretinal membrane, chorioretinal scarring, retinal detachment, etc.) but in some cases the fundus exam is near normal or perhaps

![Figure 1. Automated perimetry shows enlargement of the blindspot.](image1)

![Figure 2. Spectral-domain OCT shows attenuation of the IS/OS junction between the fovea and optic disc.](image2)

![Figure 3. Multifocal ERG shows flattening of the 3D plot.](image3)
completely normal. Although it is not within the scope of this manuscript to describe other ancillary testing for retinal disease, the clinician might consider macular optical coherence tomography (OCT) to look for subtle evidence for maculopathy that can escape ophthalmoscopic detection. OCT in patients with peripapillary derangement or acute zonal occult outer retinopathy (AZOOR) might show abnormalities in the outer retina (e.g., inner segment and outer segment junction, Figure 2). In addition, fluorescein angiography still has a role for detecting leakage from occult vascular pathology (e.g., macular nonperfusion or leakage from an underlying neovascular membrane). Over time even in patients who present with an occult retinopathy and a normal fundus exam, subtle or more obvious and visible retinal pigment epithelial (RPE) change might develop in the area of initial retinal dysfunction.

If the clinical symptoms are suggestive of a retinal origin or if an optic neuropathy cannot be established clinically then electrophysiologic testing might be useful. Full field electroretinogram (ERG) might show depression of waveforms for diffuse retinal dysfunction but multifocal ERG (MERG) might be necessary to detect localized macular (central or ring scotoma) dysfunction or peripapillary (big blind spot) retinal dysfunction (Figure 3). As a mass response test, the full field ERG might be normal in patients with focal, zonal, or macular only disease. I sometimes will combine the full field ERG and/or MERG testing with a visual evoked potential (VEP) if there is suspicion for nonorganic overlying or if I am deprived of the luxury of a confirmatory relative RAPD because of bilateral and symmetric ocular disease. In patients with an abnormal ERG or MERG the possibility of occult autoimmune retinopathy (e.g., autoimmune related retinopathy and optic neuropathy or paraneoplastic retinopathy (e.g., cancer associated retinopathy or melanoma associated retinopathy) should be considered. In these cases retinal antibody testing and specific paraneoplastic antibody testing might be warranted.

In this particular patient the full field ERG showed a depressed waveform and especially a lower amplitude in the b wave in the affected eye consistent with the diagnosis of the acute idiopathic blind spot enlargement syndrome (the “big blind spot syndrome”) which some authors believe is a subset of acute zonal occult outer retinopathy (AZOOR).5,6 The diagnostic dilemma often occurs in the acute setting when one of the retinal “white dot disorders” (e.g., multiple evanescent white dot syndrome or MEWDS) occurs without the “white dots” (i.e., MEWDS without the MEWDS”). In this setting, even an experienced retina doctor who sees a young female patient with acute loss of vision, an RAPD, and a normal initial fundus exam might be tempted to refer the patient to neuro-ophthalmology for an evaluation for demyelinating optic neuritis. In this patient, an MRI was performed that showed no contrast enhancement of the optic nerve (which is atypical for acute demyelinating optic neuritis) and no confirmatory white matter lesions for MS. Unfortunately, a normal MRI cannot rule out demyelinating optic neuritis especially if the study was not a fat suppressed, dedicated orbit, post-gadolinium study. Nevertheless, the normal MRI is an additional “red flag” to raise the suspicion for retinopathy over optic neuropathy in this case. The patient subsequently had mild improvement in her blind spot enlargement and did not develop any recurrence. Over time subtle RPE change appeared in the peripapillary region of the affected eye but no new visual or neurologic symptoms occurred after five years of follow up.

SUMMARY
There is considerable overlap in the clinical presentation of some acute retinal disorders and optic neuritis. The comprehensive ophthalmologist might have difficulty determining who they should call first for consultation, retina or neuro-ophthalmology. In a young otherwise healthy female with acute unilateral visual loss, pain with eye movement, and an RAPD optic neuritis is one of the top etiologies in the differential diagnosis. These overlapping demographic and clinical features between acute retinopathy (e.g., the big blind spot syndrome) and acute optic neuritis can be challenging even for the neuro-ophthalmologist. The potential differentiating clinical symptoms suggesting retinal disease are photopsias, metamorphopsia, and lack of pain with eye movement. The possibly helpful differentiating clinical signs suggesting retinal etiology are a big blind spot or ring scotoma on visual field testing, normal color and brightness, the lack of an RAPD, or an abnormal macular photostress test. A negative high quality gadolinium enhanced cranial and orbital imaging is another red flag that should raise suspicion for a retinal etiology for the visual loss. OCT and fluorescein angiography might be helpful or might be normal and the key diagnostic test for differentiating retinal from optic nerve pathology in these cases might be electrophysiography. Full field ERG might be useful for diffuse retinal disease but MERG might be necessary for focal retinal disease especially the acute idiopathic blind spot enlargement syndrome.

CME ANSWERS
1. d
2. a
3. c

REFERENCES
HOW TO DISTINGUISH PSEUDOPAPILLEDEMA FROM PAPILLEDEMA

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LEARNING OBJECTIVES
1. Review the cardinal clinical signs of papilledema versus pseudo-papilledema in patients presenting with an elevated optic nerve appearance
2. Describe the best use ancillary tests and tailor the investigative approach in patients with possible papilledema versus pseudo-papilledema

CME QUESTIONS
1. Does the patient in the case presented have papilledema or pseudo-papilledema?
2. Is this a case of optic disc drusen?
3. How can we differentiate benign causes of an elevated optic nerve appearance from causes of raised intracranial pressure?

KEYWORDS
1. Papilledema
2. Pseudopapilledema
3. Optic Disc Drusen
4. Ultrasonography
5. Fluorescein Angiography

INTRODUCTION
The differentiation of optic disc drusen (ODD) from true optic disc edema (ODE) is of critical importance, because ODE may represent a life-threatening condition requiring urgent and costly ancillary testing, whereas ODD is most often a benign process requiring only observation. In cases of ODD located on the disc surface, diagnosis may be straightforward, but with intrapapillary ODD (“buried drusen”), the optic disc appearance may mimic that of ODE. Ancillary testing has been utilized to aid in identification of ODD, including B-mode ultrasonography1, CT imaging, and fluorescein angiographic “autofluorescence.” 2-5 Recently, specific fluorescein angiography (FA) criteria for differentiating ODD from ODE have been published6. Optical coherence tomography (OCT) is also evolving as a modality for differentiation of ODD from ODE7-11.

This presentation will discuss each modality, with examples, advantages, and disadvantages for each. Findings in ODD will be compared with those in ODE.

ILLUSTRATIVE CASE
A 36-year-old obese woman reports a 3-week history of headache, increased in frequency over her baseline migraine pattern. She has occasional blurring of vision but no transient visual obscurations. She denies pulse synchronous tinnitus or diplopia. Her only medications include occasional over the counter analgesia for her headaches.

Examination shows the visual acuity is 20/15 each eye, with equivocally sluggish pupils but no relative afferent pupillary defect. Eye movements are normal as is the remainder of the neuro-ophthalmic examination except for the fundus. The optic discs are elevated, with blurred margins and no visible cup, as shown in the fundus photos (Figure 1). No spontaneous venous pulsations are observed. Visual fields demonstrate bilateral inferior constriction (Figure 2).

Figure 1

Figure 2
AUDIENCE RESPONSE QUESTION
What test would you use to determine whether this is a case of papilledema versus pseudo-papilledema?

The diagnostic test options are:

1. B-scan ultrasonography
2. Fluorescein angiography with assessment for autofluorescence
3. OCT, both time domain and spectral domain.
4. Cranial and orbital MRI with venography
5. Lumbar puncture

PANEL DISCUSSION
What would you choose as your “money test” and why?

CASE CONCLUSION
B-scan ultrasonography was negative for calcified ODD (Figure 3). Fluorescein angiography did not demonstrate autofluorescence (Figure 4). Time-Domain OCT showed nerve fiber layer thickening but no characteristic feature to differentiate ODD from ODE (Figure 5).

The entire angiographic sequence showed no early leakage, with progressive circumferential peripapillary staining with nodularity; no disc hyperfluorescence was present (Figure 6).

The findings were typical for buried ODD.

DISCUSSION
When ODD are visible on the optic disc surface, identification is straightforward. The clinical features of intrapapillary (buried) ODD include optic disc elevation, blurred optic disc margins without obscuration of peripapillary retinal vessels, and nodular border of the optic disc, in the absence of features of optic disc edema, such as retinal nerve fiber opacification with obscuration of retinal vessels, microvascular abnormalities such as optic disc surface capillary net dilation, telangiectasia, retinal hemorrhages, and exudates. In this scenario, it is not infrequently difficult to distinguish ODD from ODE with certainty.

The detection of autofluorescence of the optic disc on pre-injection photography is confirmatory for ODD (Figure 7), but the technique is most effective when the ODD are on or near the disc surface, in which case ancillary testing is unnecessary. For intrapapillary ODD, sensitivity is low; Kurz-Levin and Landau1 documented autofluorescence in only 15 of 82 (18%) cases of “buried” ODD. Computed tomography (CT) (Figure 8) is limited not only by 1.5 mm thickness of orbital sections, which often may miss ODD, but by the requirement for calcification of ODD for their detection. B-mode ultrasonography (Figure 9) similarly detects only calcified ODD. While no study has clearly identified the percentage of ODD which are calcified, Kurz-Levin and Landau1 found positive ultrasonography in only 39 of 82 (48%) of eyes with “buried” ODD.1 In the study of Pineles and Arnold, 30 eyes with proven ODD had also undergone B-scan ultrasonography, 8 of which were negative8.
Fluorescein angiography has been studied as a tool to identify ODD and differentiate from ODE. Sanders and Ffytche and Mustonen and Nieminen reported on FA findings in ODD, describing “early fluorescence” and “nodular, well demarcated late hyperfluorescence” seen without leakage. Cartlidge et al. compared the FA findings of eyes diagnosed with “pseudo-papilledema” to those of eyes with true papilledema, emphasizing the “increased vascularity seen more often in papilledema.” Others have commented on findings in ODD, and a simplified criterion of “disc leakage vs disc staining” has been the standard discriminating feature. A clear distinction between “hyperfluorescence,” staining, and leakage, a critical appraisal of intrapapillary vs peripapillary hyperfluorescence, and a comparison of the findings of the entire FA sequence between ODD and ODE was recently published. Intrapapillary ODD are characterized by either no early staining, or a characteristic early nodular staining (Figure 10a), unlike ODE, which is characterized by early diffuse leakage (Figure 10b). Intrapapillary ODD also often demonstrate a characteristic late peripapillary staining, either nodular, circumferential, or both (Figure 11a), not seen in ODE, in which capillary dilation and tortuosity, early and late fluorescein leakage (Figure 10b) are seen. Coexistent ODE and ODE may be distinguished by these features. Our case demonstrated the late nodular and circumferential peripapillary stain without leakage characteristic of buried ODD, despite a fundus appearance which suggested ODE.
Johnson et al\textsuperscript{9} suggested time-domain (TD) OCT criteria for differentiating ODD from ODE, based on the internal optic nerve contour and the subretinal hyporeflective space (Figure 12a).

More recently, Yi et al\textsuperscript{10}, Lee et al\textsuperscript{11}, and Sarac et al\textsuperscript{12} have documented that the increased resolution of spectral-domain (SD) OCT may provide a clearer image of buried ODD (Figure 12b) and may also distinguish superimposed ODE.

**SUMMARY**

FA in our case confirmed the presence of ODD without ODE. Ultrasonography, autofluorescence, and TD-OCT were not useful in differentiating ODD from ODE. The use of SD-OCT may be the preferred diagnostic modality in the future.

**CME ANSWERS**

1. Pseudopapilledema
2. Yes
3. Fluorescein angiography is an accurate and reliable method of differentiating pseudopapilledema from papilledema

**REFERENCES**

LEARNING OBJECTIVES

1. To demonstrate the utility of multi-focal visual evoked potential testing in capturing the effects of demyelination and remyelination in the afferent visual pathway of optic neuritis and multiple sclerosis patients

2. To illustrate how motion perception techniques can be used to capture visual perception disturbances after optic neuritis

3. To highlight the potential role of optical coherence topography in detecting the effects of primary and secondary changes in retinal architecture in multiple sclerosis patients

CME QUESTIONS

1. What are four ancillary tests that can be used prospectively to capture structural changes in the anterior visual pathway in response to an inflammatory optic nerve injury?

2. How can we differentiate differences in form versus motion perception after optic neuritis?

3. How can optical coherence tomography be used to capture changes in retinal architecture in optic neuritis and multiple sclerosis patients?

KEYWORDS

1. Optical Coherence Tomography
2. Ganglion Cell Layer
3. Motion Perception Testing
4. Retinal Nerve Fiber Layer
5. Multi-Focal Visual Evoked Potentials

INTRODUCTION

Neuro-ophthalmologists have traditionally relied upon the history and physical examination to localize visual problems in their patients. While these clinical tools represent the cornerstones of our discipline, there are many ancillary testing techniques which can enhance the diagnostic process. In the following presentation, the merits of both well-established and relatively novel diagnostic tests will be discussed in the context of a typical case of optic neuritis. The relative contributions of various disease mechanisms: demyelination, axonal loss, neuronal damage, and cortical compensation will be reviewed. So too, the utility of different tests in capturing specific pathogenic processes in optic neuritis will be highlighted. Several techniques will be described with reference to the case example provided, optic neuritis; yet, the principles of how these tests may be used apply to a variety of optic nerve disorders.

Figure 2: A Baseline SD-OCT shows peripapillary retinal nerve fiber layer thickening in the left eye (180µm) relative to the right eye (103µm), which is consistent with the observed optic disc edema in the left eye in the case example provided.
Figure 3: Three months after the ON event, there is peripapillary retinal nerve fiber layer thinning in the left eye (77µm) relative to the right eye (101µm). The macular volume in the left eye remains within normal limits (9.6mm³) at the 3-month follow up point.

Figure 4: Six months after the acute ON event, there is peripapillary retinal nerve fiber layer thinning in the left eye (61µm) relative to the right eye (104µm). There is also associated macular volume loss in the left eye (9.3 mm³).
CASE EXAMPLE: OPTIC NEURITIS
A 30-year old woman presents with a 3-day history of vision loss in the left eye. She reports no other medical problems. She states that her vision loss progressed over a 72 hour period, beginning as a “smudge” in the central visual field of the left eye. She describes pain with eye movements, and notes that colors appear “washed out” in the left eye relative to the right eye. On examination the visual acuity is 20/20 in the right eye and 20/100 in the left eye (Snellen equivalent). There is a left relative afferent pupil defect. Visual field testing with Goldmann perimetry shows normal results in the right eye and a cecocentral scotoma in the left eye. Color vision measures 10/10 HRR pseudoisochromatic plates in the right eye and 0/10 plates in the left eye. External ocular examination, extraocular movements, and slit lamp assessment are normal. Dilated fundus examination shows a normal right optic nerve, and left optic disc hyperemia (Figure 1). Based on the clinical presentation, the patient is diagnosed presumptively with left optic neuritis (ON).

Figure 1: Dilated fundscopy shows a normal appearing right optic nerve (on left) and left optic disc edema (on right).

MEASURING THE EFFECTS OF ACUTE AND CHRONIC OPTIC NERVE INFLAMMATION IN OPTIC NEURITIS
In ON, the affected optic nerve serves as a “window” to understand mechanisms of symptom onset and recovery applicable to isolated and recurrent demyelination elsewhere in the central nervous system (CNS). There are alternations in myelin integrity and in the oligodendrocyte–axon unit in the acute and chronic phases of ON that underpin symptom onset and recovery. In addition, given the capacity for functional adaptation in the CNS, clinical recovery may arise not only as a consequence of structural repair at the site of the primary lesion, but also from compensatory changes in the afferent visual pathway at a distal location. After ON, acute cytokine release induces transient conduction block in the affected portion of the optic nerve. With intact myelination and preserved axons, the recovery occurs with removal of inflammatory mediators; and, in turn reversal of the visual deficit. The initial period of recovery is often rapid, in response to early resolution of acute inflammation. Further improvement in vision can be seen up to a year after the acute ON episode. Notably, remyelination may continue for up to 2 years, as suggested by reported progressive shortening of (initially) prolonged visual evoked potential latencies. Reorganization of cortical activation has also been reported after optic neuritis. Thus, visual recovery after ON can occur through several mechanisms: remyelination, development of continuous conduction through sodium channels that develop along the demyelinated segment, and cortical plasticity. The substrate for permanent vision loss after ON is likely disruption of axonal and neuronal integrity in the afferent visual pathway, which can arise from persistent acute inflammation and lack of trophic support from myelin.

From a functional stand-point, high and low contrast letter acuity testing, perimetry, and color vision testing can reliably quantify the acute and chronic effects of optic nerve inflammation. Acutely, vision loss is at its nadir, resulting in marked functional deficits. Over time, as inflammation abates, there is gradual recovery in visual function.

TESTS OF AFFERENT VISUAL PATHWAY FUNCTION: HIGH-CONTRAST LETTER ACUITY
High-Contrast Letter Acuity: High contrast visual acuity testing is a relatively insensitive means of capturing vision loss in the setting of most optic nerve disorders, including ON. In the Optic Neuritis Treatment Trial (ONTT), mean visual acuity 1 year after entry into the ONTT was better than 6/5 (Snellen equivalent), with less than 10% of patients manifesting visual acuity worse than 6/12. A baseline (or 1-month) visual acuity ≤ 20/50; contrast sensitivity ≤ 1.0 log units; and visual field mean deviation ≤ -15 dB have been shown to be good predictors of abnormal vision 6-months after ON.

Low Contrast Letter Acuity & Contrast Sensitivity: Numerous studies have shown that low contrast letter acuity and contrast sensitivity are sensitive means of capturing vision loss, even in patients with (Snellen vision equivalent) 20/20 vision after ON. In 2006, Fisher and colleagues conducted a cross-sectional study that compared RNFL thickness between ON-affected eyes of MS patients (MS ON eyes), MS eyes without a history of ON (MS non-ON eyes), and the eyes of disease-free controls. In addition to optical coherence tomography (OCT) measurements, they performed low-contrast letter acuity, contrast sensitivity (Pelli-Robson charts), and high-contrast visual acuity testing. The authors found that RNFL thickness was reduced significantly among MS patients (92µm) relative to control eyes (105µm, P < 0.001), with the lowest RNFL values detected in MS ON eyes (85µm, p < 0.001). Furthermore, lower visual function scores were associated with reduced mean peripapillary RNFL values in MS eyes: for every 1 line decrease in low-contrast letter acuity or contrast sensitivity score, the mean RNFL thickness decreased by 4µm. In this study, MS patients were excluded if Snellen visual acuity equivalents were worse than 20/200 in both eyes, because this degree of vision loss precluded testing of low-contrast letter acuity. Hence, there may be a more robust role for low contrast letter acuity testing in the early stages of ON.
letter acuity and contrast sensitivity in detecting subtle manifestations of vision loss in the post-acute phase of ON rather than the acute phase of optic nerve inflammation, when vision loss is more severe.

**Frequency Doubling Perimetry:** Conventional automated perimetry is a reasonable means of capturing functional defects referable to optic nerve inflammation; albeit the utility of this testing modality tends to hampered in the acute phase for patients with Snellen visual acuity equivalents worse than 20/200. In a recent consecutive case series, 20 patients with resolved ON were compared to 20 healthy controls, with the aim of examining the performance of full-threshold 30–2 frequency-doubling perimetry (FDP) in comparison with standard automated perimetry (Swedish interactive threshold algorithm 30–2 program) in patients with resolved ON. Standard automated perimetry and FDP showed general depression in the fovea and extrafoveal areas. Correlations between SAP and FDP were statistically significant for mean deviation (Pearson’s r > 0.75; p < 0.001) and pattern standard deviation (r > 0.6; p < 0.005). Defects detected with FDP were larger than with SAP in 14 eyes (70%). In follow-up after 2 weeks and again after 2 and 5 months, FDP indicated slower improvement in visual field defects in the fovea and extrafoveal areas, whereas SAP indicated rapid improvement in these defects. From their findings, the authors concluded that FDP is at least comparable with and potentially more sensitive than SAP in detecting visual field defects in resolved ON.

**Color Vision:** Color vision testing is useful in detecting disorders of the optic nerve, as often the color vision deficit is disproportionately impaired relative to the visual acuity, particularly in mild ON. For example, many patients with ON who have vision deficits in the Snellen visual acuity range of 20/20–20/50 can score poorly on Ishihara plate testing, which is sensitive to picking up red-green color loss. Alternatively, Hardy-Rand-Rittler (HRR) pseudo-isochromatic plates may be used, which have an advantage over the Ishihara method, because they are more sensitive to neuro-ophthalmic causes of vision loss, and they detect red-green and blue-yellow deficits. In a recent cross sectional study, Villoslada and colleagues studied the association between high-contrast visual acuity, low contrast visual acuity, color vision [HRR plates and Lanthony D15 (LD15) tests]; and, both high-resolution spectral-domain OCT (SD-OCT) and time domain OCT (TD-OCT) testing in a cohort of 213 MS patients (52 with previous ON) and 47 matched controls. They noted that MS patients had impairments in high and low contrast visual acuity (p < 0.001), and that they also suffered from even more profound abnormalities in color discrimination (p < 0.0001). There was a strong correlation between color vision and SD-OCT measures of RNFL thickness and papillomacular bundle thickness. Farnsworth D15 and Farnsworth—Munsell 100 hue testing are highly sensitive tests of color vision loss in the post-acute phase of ON but generally require more time than is practical in a typical clinic setting. In the case example provided, the patient had a marked deficit in color vision at the onset of symptoms in the left eye, which was commensurate with the severity of the central vision loss. Hence, color vision testing may not be particularly discriminating in patients with severe vision loss in the context of acute optic nerve inflammation. With time however, color vision deficits may be detectable in the post-acute phase of ON, even when high contrast visual acuity has returned to “normal.”

**Critical Flicker Fusion Frequency (CFF):** CFF is defined as the frequency at which an intermittent light stimulus appears to be completely steady to the observer. In a practice, patients view a flickering light to test the ability of the optic nerve to conduct impulses with uniform speed. This quick and simple test method has proven to be very useful in identifying visual loss due to optic nerve damage. In a recent study, CFF was measured in response to red and blue stimuli for ON patients and patients with diabetic retinopathy. The results showed that CFF was impaired for red stimuli in ON patients, and for blue stimuli in patients with diabetic retinopathy, which distinguished the two groups. In a second study, 25 patients (31 affected eyes) with acute ON were followed serially with CFF. The CFF results were 100% abnormal in ON eyes at initial onset, and then gradually improved over time. However, even in recovery CFF abnormalities were noted in 37% of ON eyes. There were also CFF abnormalities in the fellow eyes of patients with unilateral ON. Thus, CFF was also shown to be a sensitive indicator for detecting visual dysfunction in patients with ON and could be used to track recovery in vision over time from the acute to chronic phases of an ON event.

**TESTS OF AFFERENT VISUAL PATHWAY STRUCTURE**

Recent innovations in para-clinical testing techniques allow us to capture structural manifestations of demyelination, remyelination, axonal damage, and neuronal degeneration in ON patients.

**Optical Coherence Tomography:** Since the invention of the ophthalmoscope in 1851, the structural consequences of optic nerve injury have been visualized acutely as optic disc edema, followed by optic disc pallor and corresponding defects in the retinal nerve fiber layer (RNFL), which lacks myelin. In 1974, Frisén and Hoyt interpreted RNFL defects as axonal attrition in MS patients. The advent of OCT has allowed us to quantify changes in RNFL thickness in the immediate on convalescent phases of ON. In prior generations of OCT, high-resolution cross-sectional images of the retina were generated by an optical beam being scanned across the retina, using the principles of low coherence interferometry, which allowed the magnitude and echo time delay of backscattered light to be measured with high temporal accuracy. With the recent development of “Fourier” or “Spectral” domain OCT light echoes are detected in simultaneous fashion, increasing the sensitivity that enabling high-speed imaging with this technique. Since SD-OCT technology became commercially available in 2006, it has been possible achieve an axial image resolution of 5–7μm with imaging speeds of 25,000 axial scans per second, which is approximately 50-fold faster than the previous
Visual Evoked Potentials: The visual evoked potential (VEP) is a response of the brain to repeated visual stimulation and is recorded when visual field is stimulated with a single checkerboard pattern [full-field VEP (FF-VEP)]. The VEP is an objective means for measuring function of the visual pathway and is known to be generated at the level of striate cortex by the combined activity of post-synaptic potentials. The magnitude of the VEP reflects the number of functional afferent fibers reaching the striate cortex and the degree of synaptic activity in V1. In patients with ON, the number of functional afferent fibers is determined by a combination of two factors: the severity of the inflammation and axonal degeneration along the visual pathway. Therefore, diminished VEP amplitude indicates inflammatory conduction block, axonal atrophy, or a combination of both. The increase in amplitude, on the other hand, is a consequence of resumed conduction in previously blocked fibers due to resolution of inflammation and edema; or possibly, to expansion of synaptic activity along the visual pathway up to the level of V1. Delayed conduction of VEP is recognized as one of the earliest features of acute ON; with the subsequent shortening of latency thought to represent the process of remyelination. Clinical usefulness of the FF-VEP is limited by the fact that it provides a summed response of all neuronal elements stimulated and is greatly dominated by the macular region due to its cortical overrepresentation. Being the vector sum of numerous differently oriented dipoles, the waveform of the full-field VEP is prone to unpredictable change depending on the part of the nerve or visual field affected leading sometimes to detection of apparent rather than real latency delay and waveform distortion. A recent advance in VEP technology in the form of multifocal VEP (mfVEP) eliminates limitations of full-field stimulation by providing simultaneous, but independent stimulation of plurality of visual field locations. In a study by Klistorner and colleagues, mfVEP was used to study 25 subjects with acute unilateral ON with serial mfVEP and OCT testing over time. While mfVEP amplitude asymmetry at baseline varied significantly among the patients, it was, on average, very high, indicating considerable reduction of amplitude in the affected eye. The inter-eye asymmetry in mfVEP amplitude decreased over time indicating ongoing functional recovery. There was negative correlation between the inter-eye asymmetry of RNFL thickness and that of mfVEP amplitude at 1 month, consistent with vasogenic edema in the acute phase, causing an increase in RNFL thickness, with a corresponding reduction in mfVEP amplitude. During recovery, the correlation became progressively more robust, suggesting the diminishing role of optic nerve edema in measured RNFL thickness and unmasking the association between RNFL atrophy and low mfVEP amplitudes. The potential correlation between OCT-measured RNFL values and mfVEP measures of anterior visual pathway damage was demonstrated by the same group, who evaluated 32 patients with unilateral ON and 25 control subjects with mfVEP testing and OCT. The mean RNFL thickness in ON eyes (85μm) was reduced by 19.2% compared with control eyes (104μm) (P < 0.0001). There was a 39.8% reduction in the amplitude of the mfVEP in ON eyes relative to control eyes (P < .0001). Linear regression analysis demonstrated a strong correlation between inter-eye asymmetry values of RNFL thickness and mfVEP amplitude (r = 0.90, P < .0001). Lower RNFL values were also associated with increased mfVEP latency (r = −0.66, P < .002). In addition to demonstrating the utility of mfVEP in tracking optic nerve injury in ON patients, this study further confirmed the significant correlations between structural and functional measures of optic nerve integrity and showed that demyelination contributes to axonal loss in the anterior visual pathway. Hence, to capture the acute and chronic effects of inflammation in ON, one could pair mfVEP and OCT testing to capture the synergistic effects of acute demyelination and axonal loss over time.

Magnetic Resonance Imaging Texture Analysis: Image texture refers to a local characteristic pattern of image intensities and can be quantified using texture analysis methods with conventional magnetic resonance imaging (MRI) techniques. Texture is fine in regularized tissue, such as normal white matter; and coarse in damaged structure in MS lesions. T2 MRI texture has been shown to be a sensitive measure of tissue injury and repair in MS associated with an acute inflammatory demyelinating event, and texture property at baseline correlates with the degree of disability progression over two years in MS patients. In a recent study, ON patients and 8 healthy control subjects underwent MRI. Within 14 days of symptom onset, optic nerve lesion texture was coarser in the affected relative to non-affected eyes, and control eyes. Over time, the lesion texture became less coarse in ON eyes. Lesion texture of the optic nerve was the only variable that predicted the extent of visual recovery in the affected eyes. The findings from this study suggest that acute tissue injury as measured by image texture analysis helps predict functional recovery after optic neuritis. In the case example provided, T2 texture could be followed over time to determine to what extent the texture signal normalized, and...
how this corresponded with visual recovery in the left eye. Of
further interest, the T2 texture could be compared to mfVEP
amplitude and latency to determine whether this is a tenable
MRI surrogate measure of demyelination and remyelination in
the anterior visual pathway.

**QUESTION: HOW CAN WE DIFFERENTIATE
DIFFERENCES IN FORM VERSUS FUNCTION
PERCEPTION AFTER ACUTE ON?**

**Motion Perception Testing:** Recent studies with functional
MRI (fMRI) have shown that cortical reorganization may
play an adaptive role in visual recovery after ON, along
with remyelination in the injured optic nerve. In a study
that aimed to assess motion perception and the associated
cortical response after ON, 21 patients with were evaluated
over a 1 year period with repeat visual acuity, color
perception, visual field, contrast sensitivity, dynamic visual
function (motion perception), fMRI and VEP testing. During
motion perception testing patients were presented
with moving dot arrays and stationary dots and asked
whether they detected a movement in each stimulus. In
an object from motion (OFM) extraction, subjects viewed
motion defined objects and were asked to identify and
name the object. In ON eyes visual acuity, visual field,
and colour vision deficits were at their worse in the acute
phase, and subsequently improved after 1-month. Contrast
sensitivity deficits persisted longer, and improved
4-months after symptom onset. In contrast to routine
visual tests, motion perception was impaired during the
full follow up period of 1 year. Furthermore, fMRI studies
showed that the behavioral deficit in motion perception
was associated with reduced cortical activation during
motion processing. Thus while, previous longitudinal
studies suggested that measures of low-contrast vision
testing is a sensitive marker of visual dysfunction in MS
patients, this study demonstrated that motion perception
testing revealed the most significant and prolonged
impairment after ON. Moreover, the motion perception
problems were independent of contrast sensitivity levels.

In a follow up study, the same group aimed to identify
mechanisms underpinning the sustained deficit in dynamic
visual functions following ON. They hypothesized that
dynamic visual processes, such as motion perception, may
be more vulnerable to slowed conduction in the optic
nerve, which could be measured with VEP testing. To
explore this hypothesis they did serial motion perception
and FF-VEP testing at presentation, 1-month, 4-months,
and 12-months after ON. The FF-VEP amplitudes in ON
eyes were significantly reduced compared to fellow eyes in
the acute phase but these differences disappeared in later
phases of recovery. In contrast to static visual tests, ON
eyes demonstrated a sustained deficit in motion perception,
as evident in the OFM extraction task 12 months after
ON. Visual performance 1 month after ON was highly
predictive of visual recovery, as determined from testing
visual acuity, contrast sensitivity and OFM function. Intact
VEP amplitudes were associated with recovered
visual acuity and contrast sensitivity after ON, suggesting
that these visual functions depend on a sufficient amount
of visual information reaching the cortex. Yet, motion
perception was impaired even in patients with intact VEP
amplitudes, suggesting that an intact amount of visual
projection alone does not impact dynamic visual function. While the magnitude of contrast sensitivity improvement
related to the extent of VEP amplitude restoration, the
magnitude of OFM improvement depended on the extent
of VEP latency reduction post-ON. The authors concluded
that conduction velocity in the visual pathways correlated
closely with dynamic visual function, suggesting that there
is a need for rapid transmission of visual input to perceive
motion. Thus, motion perception testing may serve as a
tool to assess the magnitude of myelination in the visual
pathways. Moreover, implementing motion perception
testing in our standard testing procedures may allow us to
better capture the acute and chronic consequences of optic
nerve inflammation in a manner that is clinically relevant to
subjective experience of patients post-acute ON.

**QUESTION: HOW CAN WE CAPTURE CHANGES
IN RETINAL ARCHITECTURE THAT MIGHT COULD
INSIGHTS ABOUT DISEASE MECHANISMS IN ON
AND MS PATIENTS?**

Most ON patients recover vision over a period of weeks to
months, during which time optic disc pallor may evolve as a
“footprint” of the inflammatory injury, indicating axonal
loss. Traditionally, changes in RNFL have been attributed to
retrograde axonal degeneration. There is an evolving body
of literature, however, which suggests that there may be
primary and secondary changes in the RNFL “and beyond” in
MS patients, which could impact our understanding of
pathogenic mechanisms in this disease.

**Optical Coherence Tomography:** Retinal Nerve Fiber Layer
Thinning: Two to 3 months after an acute ON event, optic
disc pallor and RNFL thinning evolve, with earliest signs of
significant RNFL atrophy manifesting in the temporal RNFL
region. Recent TD-OCT studies have shown that RNFL values
continue to decrease for 6 months after symptom onset,
plateauing thereafter. Lower RNFL values correlate with
reduced visual acuity, visual field mean sensitivity, and color
vision testing scores after ON. There are also strong
correlations between the extent of RNFL thinning after ON,
delayed mfVEP latencies, and reduced mfVEP amplitudes,
implicating a direct relationship between the severity of
acute inflammatory demyelination and consequent axonal
loss. In a recent meta-analysis of TD-OCT studies (2,063
eyes) comparing eyes with MS and ON to the eyes of
healthy controls showed an estimated average RNFL loss of
20.4µm in ON eyes. There was an estimated RNFL loss of
7.1µm in non-ON eyes of MS patients relative to control
eyes. Primary Retinal Damage: Recent work by Green
and colleagues provided the first large-scale pathological
description of retinal involvement in MS patients (n=82),
including patients with different subtypes, ages, and stages
of disease severity. In this study, changes were seen not
only in the RNFL and retinal ganglion cell layer, but also in the inner nuclear layer, suggesting that retinal injury is more widespread than previously appreciated in MS. From these findings the authors postulated that exploring the relationships between the different types of retinal pathology may aid us in understanding the factors that drive both inflammation and tissue atrophy in MS. Subsequent SD-OCT studies have explored the hypothesis that retinal damage may be a primary mechanism of injury in MS. SD-OCT studies have explored the hypothesis that retinal pathology in a subset of patients with MS.

controls. These findings supported the possibility of primary retinal pathology in a subset of patients with MS. In related work the same group reported SD-OCT—measured thinning in the ganglion cell layer of eyes affected by acute ON, and 6 months after onset (P < 0.001). No pathology was seen in the inner or outer nuclear layers of ON eyes, suggesting that retrograde degeneration after ON may not extend into the deeper retinal layers. Baseline ganglion cell layer thickness did not demonstrate swelling when compared with contralateral unaffected eyes, whereas peripapillary RNFL edema was observed in ON eyes (P = 0.008) and decreased over the course of this study. Of all patient groups investigated, those with neuromyelitis optica and a history of ON exhibited the greatest reduction in ganglion cell layer thickness. From their findings the authors concluded that axonal injury may cause neuronal pathology in MS patients. Finally, Green and colleagues detected microcystic macular edema with SD-OCT in 15 of 318 (4.7%) MS patients who harboured no other established reason (drugs, co-morbidities) for this finding. The microcystic edema predominantly involved the inner nuclear layer of the retina and tended to occur in discrete patches. They postulated that the presence of microcystic macular edema in MS suggests that there may be breakdown of the blood-retinal barrier and tight junction integrity in a part of the nervous system that lacks myelin.

**SUMMARY:**
With advances in ocular imaging, evoked potential testing, motion perception techniques, we may be able to improve upon our approach to the localization and diagnosis of many neuro-ophthalmic problems. Yet, it should be reiterated that the role of these tools is to complement; not supplant the clinical examination.

### CME ANSWERS

1. Any combination of high and low contrast letter acuity; contrast sensitivity, color vision testing (with Ishihara plates, HRR pseudoisochromatic plates, LD15 color desaturation tests), perimetry, CFF, T2 Texture analysis with MRI, OCT measured RNFL thickness/macular volume, mfVEP amplitude and latency.

2. Motion perception testing.

3. Spectral domain OCT measures of RNFL thickness; retinal segmentation techniques showing thinning of the inner and outer nuclear layers of the retina; and in the case of ON, secondary ganglion cell layer thinning.

### REFERENCES


HOW TO CAPTURE DISEASE ACTIVITY IN THE LONGITUDINAL FOLLOW-UP OF OPTIC NEUROPATHIES?

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LEARNING OBJECTIVES
1. To understand clinical tools for documenting optic nerve function
2. To establish that no one test is perfect for all individual patients with optic nerve dysfunction
3. To review the advantages and disadvantages of each optic nerve assessment technique

KEYWORDS
1. Optic Nerve
2. Optical Coherence Tomography (OCT)
3. Visual Evoked Potential (VEP)
4. Visual Acuity
5. Perimetry

INTRODUCTION
Optic neuropathy is a common neuro-ophthalmic diagnosis. Although it is often easy enough to recognize and anatomically localize in its typical forms, it is more challenging to precisely follow for any significant change over time. Many of the tools we use to evaluate and follow optic nerve function are psychophysical such as acuity and perimetry, and accordingly suffer from subjectivity and variability-related errors. The pupil is useful in optic nerve assessment, and although objectively judged by the physician, it is infrequently quantified, and thus less suitable as a long-term follow up marker. Imaging and electrophysiology provide objective metrics for optic nerve anatomy and physiology, but may be cumbersome, expensive, or demonstrate unfavorable sensitivity, specificity and variability across clinics and visits. There is no ‘perfect’ or gold standard clinical measure of optic nerve function, and the clinician must rely upon different combinations of these tools in individual patients to reliably detect meaning visual change.

CME QUESTIONS
1. Which of the following is an objective assessment of optic nerve function?
   a. Visual acuity
   b. Color vision
   c. Visual fields with confrontation
   d. Pupil assessment
   e. Visual field with Humphrey perimetry

2. Which of the following is a true advantage of visual evoked potential (VEP) testing?
   a. It is easily reproduced in any office setting
   b. It provides an objective assessment of optic nerve function without regard to patient cooperation
   c. It provides a real time assessment of optic nerve physiology
   d. It can capture not only central but also peripheral visual function information

3. What is a true disadvantage of optical coherence tomography (OCT)?
   a. It has the ability to provide objective anatomic information
   b. The time delay required for OCT to reflect an optic nerve insult’s effect on anatomy
   c. The easy correlation between the overall RNFL and meaningful optic nerve function
   d. It is a low cost technology

Case: A 40-year old woman with a known non-secreting pituitary macroadoma (with radiological evidence of chiasm compression) presents for repeat neuro-ophthalmic assessment. She has previously demonstrated no significant impairment in high contrast visual acuity, color vision, or visual field function. Best-corrected Snellen visual acuity is 20/20 in both eyes. Pupils measure 5mm in darkness and constrict to 3mm in bright light, with no relative afferent pupil defect. Color vision measures 10/10 HRR pseudo-isochromatic plates in both eyes. Ocular motility is normal. Fundus examination shows normal appearing optic nerves. Repeat automated perimetry shows some worsening of her visual field suggesting possible enlargement of the pituitary lesion.

Question: What tests can be used to capture disease progression in this patient?
PSYCHOPHYSICAL TESTS

High Contrast Visual Acuity: Visual acuity is defined as the "spatial resolving capacity" of the eye, and represents the most commonly used tool to assess visual function including that related to optic neuropathies. There are numerous charts used for visual acuity testing, but the most commonly employed are the Snellen and Early Treatment Diabetic Retinopathy Study (ETDRS) charts. Of the two, the Snellen chart is the current standard for measurement of visual acuity in clinical practice. The chart has letters of different sizes arranged from largest at the top to smallest at the bottom, which are read, one eye at a time, at a distance of 6 meters or 20 feet. Snellen acuities are usually expressed as a fraction with the numerator equal to the distance from the chart and the denominator being the size of the smallest line that can be read. High contrast letter acuity has many advantages including rapid administration, and ease of understanding and translation to lay public. Ideally, this psychophysical test should give a precise, reproducible result that is impervious to external factors; but, in reality several disadvantages exist including variability between offices (and even between exam rooms in the same office), function pertaining to central vision only, subjectivity of testing which can be easily manipulated by the patient, reliance on black-on-white high-contrast letters with diminished generalizability to real life visual acuity function. Snellen charts, in particular are hindered by variable letter size, with varying numbers of letters per line. The poor vision lines (20/200 and 20/400) usually mean that not being able to read 1 letter on the good acuity, the tester uses a "line assignment" method. This means that not being able to read 1 letter on the good acuity lines has less effect than missing 1 letter on the poor vision lines. Thus, a loss or gain in a line of vision with Snellen testing does not have the same meaning in different parts of the chart. Another disadvantages of high contrast Snellen visual acuity testing include the fact that the letters on a chart are not always the same legibility. Some letters (e.g., C, D, E, G, O) are easier to read than others (e.g., A, J, L); and the distance between letters and rows is not standardized. Finally, the term "Snellen chart" has never been standardized, and consequently, Snellen charts from different manufacturers may use different fonts, different letters, and different spacing ratios, and they may be illuminated or projected differently. Because if the deficiencies of Snellen visual acuity testing, ETDRS charts have become the "gold standard" for most current clinical trials. In neuro-ophthalmic practice high contrast letter acuity as determined by Snellen or ETDRS method is a relatively crude metric of optic nerve dysfunction, as patients can have profound deficits of visual field and color vision function and maintain 20/20 vision.

Low Contrast Letter Acuity/Contrast Sensitivity: Low-contrast acuity appears to mimic real life visual function with rarity of high contrast objects of regard. Although it is more sensitive to most optic nerve disease, it remains subjective. The utility of low contrast letter acuity and contrast sensitivity testing has been exemplified in following optic neuritis and MS patients. Three contrast levels have been used in MS trials and research studies, including 100% (high-contrast, used to measure visual acuity as a descriptor of the study cohorts), 2.5%, and 1.25% (lightest contrast level). Visual improvement as determined by the low-contrast acuity chart has been defined as a 7-letter change in score; and a 5-letter change in high-contrast visual acuity is now considered clinically significant. This threshold represents a change that exceeds what would be expected from repeated testing when there was no real change in visual acuity, and correlates with retinal nerve fiber layer (RNFL) loss in patients with MS. Furthermore, these 5- and 7-letter mean changes have been shown to correlate significantly with vision-specific and overall quality of life measures in MS patients.

Visual Field: Perimetry has evolved through stages since original confrontation-based techniques to allow quantification and statistical analysis in its currently used computerized forms. This provides critical information about visual function including both central and peripheral channels, and many of the perimeters in common use today are readily available in most cities around the developed world allowing for easier comparisons across offices over time. Despite these advantages, perimetry remains a subjective technique and significant variability exists even in very reliable subjects with optic nerve dysfunction. In a prospective case control study, 17 patients with ON and 10 healthy control subjects underwent intraday and interday repeat perimetry testing (five Humphrey 30-2 tests were administered during a 7-hour period on the same day and at the same period on 5 separate days). Patients with ON demonstrated variations in visual field sensitivity that were outside the entire range of variability for normal controls. These variations occurred for multiple tests performed on the same day, at specific times; and for tests performed at specific times on different days. Thus, when using automated perimetry to follow ON patients with visual field defects, distinguishing true systematic changes in sensitivity from variability should be undertaken with caution; and requires more than comparing a current visual field test with the most recent previous visual field test.

Pupil Response: Pupil response driven perimetry has the potential to capture widespread information concerning optic nerve function based on objective pupil reactivity, but this is not widely available or standardized, and the variable effect on pupil-related retinal function based on specific pathology remains to be elucidated. The relative afferent pupil defect (RAPD) is the quickest objective bedside test for the documentation of asymmetric optic neuropathy. The test is objective, but not often quantified, which renders it less useful in serial assessment of optic neuropathies. In addition, optic nerve dysfunction in the fellow eye can diminish or eliminate an RAPD, however in this scenario, a decreasing or resolving RAPD indicates clinical worsening.
OCULAR IMAGING

Optical Coherence Tomography: Optical coherence tomography (OCT) offers an objective, non—invasive, and highly sensitive means of quantifying axon loss in the anterior visual pathway due to any optic nerve injury, irrespective of the mechanism involved. Recent studies have shown that retinal nerve fiber layer (RNFL) values often increase during the acute phase of an optic nerve injury, particularly when there is visible optic disc edema, as in the case of anterior ischemic optic neuropathy (AION). Furthermore, OCT testing reveals that mild increases in RNFL thickness frequently occur in the context of presumed retrobulbar optic nerve injuries, which may not be apparent with standard ophthalmoscopy techniques. With time, often 3–6 months after the acute optic nerve insult, optic nerve atrophy and RNFL thinning ensue. Thus OCT is a sensitive means of detecting occult optic nerve insults, which may escape clinical detection. Therefore, OCT may represent a marker for axon loss in the anterior visual pathway caused by: optic neuritis, neuromyelitis optica, traumatic optic neuropathy, compressive lesions, ischemic optic neuropathy, toxic damage to the optic nerve, papilledema due to raised intracranial pressure, optic disc drusen, and inherited disorders of the optic nerve.

Previous studies have evaluated the role of OCT in characterizing RNFL changes due to anterior visual axis compression. The predictive value of baseline RNFL thickness for visual recovery post—surgical intervention has been studied in patients with known parachiasmal lesions. Danesh Meyer and colleagues,4 studied 40 patients undergoing surgical resection for parachiasmal lesions prospectively, and performed OCT testing before and after surgery. Patients with normal preoperative RNFL had significant improvement in visual acuity scores after surgery [from 20/40 to 20/25 (P = 0.028)], whereas patients with RNFL atrophy did not improve [(20/80 to 20/60, P = 0.177)].4 Similarly, patients with preserved pre-operative RNFL values showed greater improvement in visual field function after surgery than did patients with evidence of RNFL atrophy (-15.3 dB before and -13.3 dB after surgery, p = 0.191).4 These authors noted that eyes with severe visual field defects but normal preoperative RNFL thickness showed significant improvement after surgery.4 The results of this study suggest that patients with objective measurable RNFL loss at the time of surgery for chiasmal compressive lesions are less likely to have return of visual acuity or visual field function after surgery. The findings of Danesh—Meyer et al4 were supported by the results of a second study, which evaluated 19 consecutive patients with pituitary adenomas to determine whether OCT may offer a reliable prediction of visual outcome after medical or surgical decompression for anterior visual axis compression.2 Jacob and colleagues5 studied 17 patients who underwent trans—sphenoidal surgery and 2 patients treated with dopamine agonists. Visual field testing and OCT were performed before and after treatment. In eyes with a visual field defect before treatment, the odds of complete recovery after three months was multiplied by 1.29 for each 1-micron increase in mean RNFL thickness (odds ratio [OR], 1.29; P = 0.037).5 These data suggest that OCT—measured RNFL values may be used to predict the potential for visual recovery for compressive injuries of the anterior visual axis, such that preserved RNFL integrity increases the likelihood that visual function will improve after the intervention.5

In patients with papilledema caused by idiopathic intracranial hypertension (IIH), it would be expected that RNFL values would be elevated at the time of presentation when optic disc edema is maximal; and, in turn, decline with resolution of optic disc swelling over time. Accordingly, in a prospective study, Rebolleda and colleagues6 studied peripapillary RNFL thickness with in patients with mild papilledema associated with idiopathic intracranial hypertension (IIH). Patients underwent OCT testing at diagnosis; and 3, 6, and 12 months after presentation.6 At the time of diagnosis, RNFL thickness was 183.3 +/- 74µm and 74.9% (78.5µm) greater than in control eyes. Mean RNFL thickness values in all quadrants were significantly greater in eyes with papilledema.6 The RNFL thickness decreased significantly, as visual field function improved at each follow-up visit.6 Regression analysis showed that for every 10µm of mean RNFL thickness increase at baseline, there was a 0.6-dB decrease in visual field function at the last follow-up visit.6 Therefore, peripapillary RNFL thickness quantitatively correlated with visual field sensitivity losses in IIH. From their findings, the authors suggest this data support the application of OCT as a noninvasive method to monitor patients with papilledema.

Optical coherence tomography has also been used to track RNFL changes from in the acute and chronic phases of non-arteritic ischemic optic neuropathy (NAION). Contreras and colleagues7 used OCT to study 27 patients with NAION at baseline, 6-weeks; and 3, 6, and 12 months after presentation. The initial mean RNFL thickness (200.9µm) was increased by 96.4% increase relative to the fellow eye.7 Percentages of RNFL loss 3, 6, and 12 months after onset were 38.9%, 42.3%, and 43.9%, respectively.7 Using regression analysis, it was found that for every 1-µm of mean RNFL thickness lost there was a 2-dB decrease in visual field function.7 Furthermore, there was a 1-line drop in Snellen visual acuity for every 1.6µm deficit.7

Retinal nerve fiber layer atrophy has been demonstrated in patients affected by Leber’s hereditary optic neuropathy (LHON), and in carriers for this disorder. Savini et al6 used OCT to study RNFL thickness in unaffected carriers with LHON mutations. Sixty-six unaffected carriers (44 females and 22 males) were analyzed and compared with an age—matched control group of 70 patients (40 females and 30 males).6 As compared to the control group, unaffected male carriers showed thicker RNFL measurements in the temporal and inferior RNFL quadrants and in the 360 degrees average
CASE CONCLUSION: TO BE PRESENTED.

SUMMARY
Optic nerve anatomy and physiology often change in predictable ways with disease, and no single modality embodies the ideal tool or captures all the useful clinical information for all patients over time. All the currently available modalities have advantages and disadvantages defining their role, and the adept neuro-ophthalmologist needs to be facile with the use of all these techniques in order to properly capture clinical follow up information and make informed management decisions.

CME ANSWERS
1. Pupil assessment
2. It provides a real time assessment of optic nerve physiology
3. The time delay required for OCT to reflect an optic nerve insult’s effect on anatomy

REFERENCES

Electrophysiology
Visual Evoked Potential (VEP): VEP can provide useful information about optic nerve function, but is rarely useful in serial assessment. In addition, inter-lab differences, dependence on patient cooperation, and test-retest variability diminish its utility in tracking meaningful optic nerve changes. Multi-focal VEP (mFVEP) provides more detailed information about optic nerve function, but suffers from similar drawbacks as a serial tool to detect meaningful change, especially between labs.

Magnetic Resonance Imaging and Computed Tomography
Although MRI of the orbits has the ability and emerging resolution to quantify optic nerve anatomy, practical considerations including cost and time prevent this from becoming a mainstream serial clinical tool. CT has similar limitations in addition to radiation risks. Given these disadvantages, it is extremely unlikely that these techniques will gain widespread usage.

Electrodiagnosis
Quantitative retinal imaging techniques have vastly improved the ability to quantify optic nerve anatomy, which has a complicated relationship with optic nerve physiology and function. Perhaps the major immediate advance these techniques offer is the replacement of the ‘old style’ optic nerve descriptors such as ‘mild temporal pallor’ (a descriptive system that lacks precision, inter-rater reliability, accuracy or serial usefulness) with micron-level quantification of optic nerve and retinal anatomy. This precise quantification offers advantages over qualitative photographic documentation. This quantified assessment of the optic nerve is necessarily detailed in order to capture the most useful information; overall assessment of the RNFL is rarely as useful as quadrant or sector data. Accordingly, the use of retinal imaging as study outcome has advantages, but is dependent upon the time of testing.

Quantitative retinal imaging measurements. These differences reached statistical significance in subjects carrying the 11778 mutation, whereas only a trend was detected in those with the 3460 mutation. Unaffected female carriers had an increased thickness in the temporal quadrant when compared with the control group (P = 0.003). The increase in temporal sectors was statistically significant in females with the 11778 mutation, whereas a trend was detected in those with the 3460 mutation. A thickening of the temporal fibers was detected in all subgroups of unaffected carriers.

Unaffected female carriers had an increased thickness in the temporal quadrant when compared with the control group (P = 0.003). The increase in temporal sectors was statistically significant in females with the 11778 mutation, whereas a trend was detected in those with the 3460 mutation. A thickening of the temporal fibers was detected in all subgroups of unaffected carriers.
MURPHY’S LAW: WHEN GOOD TESTS GO BAD!

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LEARNING OBJECTIVES
1. Identify potential pitfalls with interpretation of optical coherence tomography (OCT)
2. Become familiar with sources of error using multifocal electroretinography (mfERG)

CME QUESTIONS
1. Which of the following most likely causes attenuation of the central ring 1 on the mfERG?
   a. Inadequate dark adaptation
   b. Inadequate light adaptation
   c. Eccentric fixation
   d. Epiphora
2. Which of the following is the most likely cause of a thinned RNFL in a patient with acute papilledema?
   a. Signal strength of 10
   b. Refractive error of +3.00 diopters
   c. Segmentation errors
   d. Nerve fiber layer loss from papilledema

KEYWORDS
1. Optical Coherence Tomography
2. Multifocal Electroretinogram
3. Artifact
4. Optic Neuropathy
5. Retinal Nerve Fiber Layer

INTRODUCTION
For decades, clinicians have utilized office-based testing such as fluorescein angiography, b-scan ultrasonography, and full-field ERG in the diagnosis and management of neuro-ophthalmic disorders. More recently development of optical coherence tomography (OCT), multifocal electroretinography (mfERG), and fundus autofluorescence (FAF) have improved the diagnostic armamentarium. However, as with all testing, faith in and dependence upon these tests can lead to delayed or missed diagnoses secondary to artifact, poor quality results, and misinterpretation. This syllabus will describe some of the key issues that lead to errors in selected office-based test results and diagnoses.

Case 1. Two months prior to presentation, a 30-year-old man developed sudden bilateral visual loss while driving. He had used crack cocaine just prior to getting into the car. He denied any pain or headache. The vision loss had not progressed. His visual acuities were 20/150 OU. He identified all of the Ishihara color plates. His pupils were mildly sluggish OU without an RAPD. Visual field testing showed bilateral central scotomas (Figure 1).

His fundus examination showed mild RPE changes and possible temporal pallor. Brain and orbital MRI showed normal results. Fluorescein angiogram was interpreted as normal. Time-domain OCT RNFL showed normal results. Multifocal ERG demonstrated attenuation of the central waveforms (Figure 2).

Multifocal ERG. The individual mfERG waveforms are derived by cross correlative mathematics from the continuously recorded retinal electrical activity, as measured by the corneal electrode, as compared to a 61 or 103 scaled hexagon stimulus array which changes every 13.3 milliseconds. Depending on the number of hexagons in the display, software derives either 61 or 103 waveforms. The stimulus is designed to test the central 50 degrees of visual field if viewed at 1/3 of a meter. The frequency of the stimulus change exceeds the ability of the rods to respond therefore the mfERG waves represent only central cone function. The ganglion cells do not make a significant contribution to the mfERG therefore it can be used to distinguish central loss of retinal origin from that of optic nerve origin. The mfERG is particular helpful for testing patients with focal visual field defects and patients with hydroxychloroquine retinopathy (1,2)
Several sources of potential error exist with mfERG testing. Since the electrode does not distinguish between sources of electrical activity, the test remains sensitive to any excessive muscle firing (particularly blinking and eye movements). These movements can result in increased noise. Contamination with 60 cycle electrical activity can also result in noise. Unfortunately, unlike the OCT, the mfERG has no simple quality measure and requires the technician and the interpreter to determine whether the results are acceptable or not. It is important to review the 3D plot to determine the quality and location of patient fixation by looking for the presence of a blind spot and its location. Although the mfERG requires the patient to be light adapted, according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards, testing should be avoided within 15 minutes of bright light exposure such as fundus photography or funduscopy (2). Bright light exposure can result in artifactual attenuation of the mfERG waveforms, and this affects the central hexagon disproportionately (unpublished data). Some disorders, such as melanoma-associated retinopathy (MAR) affect rod rather than cone bipolar cells. The cone-driven response of the mfERG may show normal results in MAR. Finally, patients with a central scotoma may not see the central fixation target within the mfERG stimulus. If the technician does not recognize this, the patient may fixate eccentrically to identify the target. The mfERG is exquisitely sensitive to eccentric fixation (1) and will demonstrate abnormal results centrally and may show supranormal results in adjacent hexagons.

Case conclusion. In Case 1, serologic testing revealed the following abnormalities: B12, 207 pg/ml (nl >210); methylmalonic acid, 0.49 umol/L (nl 0—0.40); homocysteine 115.5 umol/L (nl 4—12); and rbc folate, 172 ng/mL (nl...
The patient was diagnosed with nutritional optic neuropathy. Oral B6, B12, and folate supplementation resulted in the patient’s acuity improving to 20/30 OU. The visual field defects resolved, but foveal thresholds remained 30 dB OU. Closer examination of the mfERG in Figure 2, shows that the waveforms superior to fixation are larger than normal consistent with eccentric fixation.

**Case 2.** A 34-year-old woman presented with severe holocranial headaches x 2 years. She described intermittent pulse-synchronous tinnitus. She denied diplopia or transient visual obscurations. She was 5 ft tall and weighted 142 lbs (BMI = 27.7 kg/m²). Her visual acuity was 20/20 OU. Her pupils, color vision, extraocular motility, and slit lamp examination were normal. The optic discs appeared elevated and cupless, and showed no spontaneous venous pulsations (Figure 3). Automated perimetry demonstrated normal results OU. Brain MRI and MRV were not available for review, but the reports described normal results. Spectral domain OCT of the right eye showed mild thickening of the RNFL inferiorly and nasally and borderline thinning temporally. The left eye demonstrated of the superotemporal and mean RNFL compared to age-matched controls.

**Optical coherence tomography.** OCT has become a major diagnostic tool in the field of neuro-ophthalmology. The OCT records multiple reflected axial images from the ocular tissues and combines them into a single. It is most often utilized to assess and follow retinal nerve fiber layer (RNFL), to image the macula qualitatively (e.g., cystoid macular edema), and to determine the integrity of the outer retinal architecture (e.g. inner segment/outer segment (IS/OS) junction).

Numerous sources of error can occur with the use of OCT. These generally can be divided into patient, user or interpretation issues. Poor signal quality represents a common source of problems and results from media opacity (cataract, corneal clouding or exposure, vitreous haze), eye movement or blinking, and poor pupillary dilation (3,4,5). Some OCT machines describe a quantitative measure of scan quality (e.g. signal strength) in the output, while others do not. Both groups of machines depend upon the user to either accept the images or try to obtain better ones. Poor signal quality results in thinner RNFL and macular volume measurements. It can also make it difficult to see the IS/OS junction, which could be mistaken as attenuation or loss.

Other patient related issues include high refractive error (> 6D of spherical error and > 3D of astigmatism), which affects the “true” RNFL measurements because the calculations of 3.4 mm diameter measurement circle of
RNFL depend upon an ideal eye with an axial length 24.5mm. Long eyes tend to produce thinner RNFL measurements. Most OCT machines describe a normative database between 18 and 85 years of age. Since OCT measurements vary with age, the database may lack accuracy among children and the elderly. Race plays a role in OCT findings. African Americans, Caucasians, and Asians have significantly different optic disc parameters. The Heidelberg Spectralis notes that their database is only accurately compared to Caucasian individuals. Finally, debate exists on whether the optic disc size affects the true RNFL measurement (6,7,8). Intuitively, a fixed RNFL circle of 3.4 mm depends upon the distance to the edge of the optic disc, and the RNFL becomes thinner the further from the disc edge (see Figure 5). Others argue that the axial length alone makes the disc vary in apparent size and that axial length rather than true disc size modifies the RNFL. Even if the axial length is truly the culprit, clinicians rarely measure the axial length and no conversion factor to account for it is commercially available.

User errors include poor centration on the optic disc/ macula or poor centration on the visual axis. Poor centration on the disc causes some sectors/quadrants of the RNFL to appear thicker and the opposite areas thinner. Fortunately, an infrared image of the area sampled is produced for the printout allowing the clinician to determine how well the photographer centered the OCT measurement. Some OCT machines allow the user to redefine the macular centration post-processing to get an accurate central foveal thickness. Recently, Hariri et al. compared macular OCT that entered the pupil along the visual axis to ones that entered eccentric to the visual axis (9). Both OCT groups focused upon the fovea. The eccentrically obtained scans showed much thicker macular volumes and thicknesses compared to the scans through the center of the pupil. The user can identify these scans by looking at the A-scan, which will be tilted (e.g. left side higher) rather than horizontally across.

Interpretive errors abound because interpretation requires judgement regarding pathophysiology, understanding of the OCT and its limitations, and determination of errors listed earlier. The OCT does not reliably distinguish true vs. pseudodisc edema. While statistically the mean RNFL is much thicker in the true disc edema group, the groups overlap significantly (10). It is possible to follow the RNFL of a suspicious disc. Progressive thickening of the RNFL over time would indicate true disc edema instead of pseudodisc edema. This raises the questions, “What is the test-retest reliability?” and, “How much change is fluctuation vs. true change?” The answer remains unclear and varies by individual patient and device, but a general rule of thumb is a change of 10 microns for the mean RNFL. Some devices have eye registration and eye tracking software, which improve test-retest reliability. Without this software, it becomes difficult to assess for change in quadrants let alone sectors. Finally, one large source of error involves segmentation errors (11). OCT machines use algorithms to identify retinal layers. Unfortunately, these algorithms can break down in eyes with significant pathology and sometimes in “normal” eyes. The OCT determines RNFL or macular thickness by identifying certain layers of the retina and measuring the distance between them (varies by machine). These segmentation errors can be subtle affecting a small area of the A-scan but the result may show that area of the RNFL as artifically thick or thin. The clinician needs to identify when these segmentation errors occur, because the patient may erroneously receive a diagnosis of optic atrophy or edema. Some machines allow the user to correct these errors postimaging, while others do not.

**Case conclusion.** In case 2, B-scan ultrasound did not show evidence of optic disc drusen. The MRI/MRV images showed a partial empty sella and narrowing of the distal transverse sinuses bilaterally. Lumbar puncture in the left lateral decubitus position showed an opening pressure of 31 cm H2O. The rest of the CSF was unremarkable and the patient was diagnosed with idiopathic intracranial hypertension. Review of the OCT shows that the discs are small and the area of edema does not extend to the 3.4 mm scanning circle. Additionally, the “waveform” in the left eye (arrow) shows a lot of noise compared to the right eye (arrowhead), which suggests the thinning may not accurately reflect the true RNFL. The Spectral domain OCT used does not have a measure of quality listed on the output (e.g. signal strength on other spectral domain machines).

**CME ANSWERS**

1. c. The True Fovea is Not Aligned with Ring 1 and Therefore the Response in Ring 1 is Calculated From the Parfoveal Region. This Leads to an Attenuated Response (12).

2. c. While Optic Atrophy Can Occur From Papilledema, in the Acute Situation, The OCT Is More Likely to Show Thinning of the RNFL Because of Segmentation Errors.

**REFERENCES**

3. van Velthoven ME, van der Linden MH, de Smet MD, Faber DJ, Verbraak FD. Influence of cataract on optical coherence tomography image quality and retinal thickness.


