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

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 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.

Figure 2. Spectral-domain OCT shows attenuation of the IS/OS junction between the fovea and optic disc.

Figure 3. Multifocal ERG shows flattening of the 3D plot.
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 overlay 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 abnormalities in the outer retina (e.g., inner segment and outer segment junction). In addition, high quality gadolinium enhanced cranial and orbital MRI might be helpful or might be normal and the key diagnostic test for differentiating retinal from optic nerve pathology in these cases might be electrophysiology. 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**