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Clinical Challenges

Famous

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(In keeping with the format of a clinical pathologic conference, the abstract and key words appear at the end of the article.)

1. Case report

A 62-year-old white female presented to her ophthalmologist to establish eye care. Her ocular history was significant for optic neuritis OD 40 years before and glaucoma OU. Her past medical history was significant for multiple sclerosis (MS), hypertension, trigeminal neuralgia, gastroesophageal reflux, seasonal allergies, and depression. She was taking diltiazem, carbamazepine, omeprazole, cetirizine, and dimethyl fumarate. Visual acuity with correction was 20/20 OD and 20/25 OS. Intraocular pressures were 19 mm Hg OU. Pupils were equal without a relative afferent pupillary defect. Confrontation visual fields were full OU. Extraocular movements were full OU; color vision was intact OU. Amsler grid testing was normal OU. Slit-lamp examination was notable for trace nuclear sclerosis OU. Dilated fundus examination showed optic nerve pallor OD with a cup-to-disk ratio of 0.65. The optic nerve OS was normal in appearance with a cup-to-disk ratio of 0.2. The macula, vessels, and peripheral retina were normal OU.

What further work up, if any, is needed for the right optic nerve pallor?

2. Comments

2.1. *Comments by Fiona Costello, MD, FRCP*

The "law of parsimony" has taught us as clinicians to make the fewest assumptions, and seek a unifying explanation that accounts for all aspects of a case. Yet, "Hickam's Dictum" rightly argues that "a patient can have as many diseases as they damn well please."[A] This counterpoint to Occam's Razor is worthy of consideration, because even for a patient with MS, optic atrophy is a description, not a diagnosis. Therefore, the decision to pursue or defer further investigations in this case depends on whether the hypothesized mechanism of vision loss accounts for all of the clinical findings. In this context, the answer is no, because important information is missing.

First and foremost, patient-related factors need to be further explored. Not all subtypes of MS are associated with the same propensity to develop clinically overt optic neuritis. Although optic neuritis is the first clinical manifestation for 20% of individuals who go on to develop relapsing-remitting

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MS,[18] it is an uncommon event for primary progressive MS patients.[8] Disease duration is also a factor to consider, because most patients with relapsing-remitting MS will go on to develop secondary progressive disease over the course of their lifetime. At this point, patients no longer experience clinically overt relapses but will often demonstrate signs of afferent visual pathway damage (optic disk pallor; prolonged visual evoked potential latencies; reduced optical coherence tomography [OCT]-measured retinal nerve fiber layer, macular volume, and ganglion cell layer values). Interestingly, the patient in question is in her seventh decade of life, albeit she is still being treated with a disease-modifying agent (dimethyl fumarate), which is more commonly used in the relapsing phase of MS. Among relapsing-remitting MS patients, subclinical afferent visual pathway involvement in common; in fact optic nerve pathology is ubiquitous, with up to 99% of MS patients demonstrating demyelinating optic nerve lesions at postmortem.[27] Therefore, the lack of an observed relative afferent pupil defect might reflect the fact that both optic nerves have sustained damage over time. Because the patient has other comorbidities, she is also vulnerable to mechanisms of optic nerve injury unrelated to MS. In keeping with the law of parsimony, I would seek corroborating evidence to support the diagnosis of optic neuritis, and also the reported history of glaucoma, because it has been my experience that normal tension glaucoma may be presumed in some patients, particularly if aspects of their medical history are not known, or overlooked. This patient does not use treatment for glaucoma, which would prompt further skepticism on my part, as would the description of a cupped, atrophic optic nerve on the right, and a normal appearing optic nerve on the left. Asymmetric optic disk cupping would be considered atypical in glaucoma. Moreover, other causes of optic nerve injury can be associated with nonglaucomatous cupping of the disk including compressive optic neuropathies, ischemic optic neuropathy, and notably optic neuritis.[26,34]

Second, the pattern of vision loss needs to be better characterized to help localize the cause of the right optic neuropathy. This patient is stated to have a history of right optic neuritis, yet there is no mention of comparative color perception desaturation or a relative afferent pupil defect in this eye. These absent features may reflect bilateral optic nerve damage, caused by MS. Absent from this evaluation is formal perimetry, which is needed to better quantify the visual function of both eyes. Keltner and colleagues evaluated 10,443 visual fields obtained from 454 patients in the original Optic Neuritis Treatment Trial and reported that during years 1 through 15 the affected and fellow eyes exhibited predominantly localized loss in the nerve fiber bundle region (partial arcuate, paracentral, and arcuate defects).[12] At year 15, 39.5% of abnormalities in the affected eyes and 26.3% in the fellow eyes consisted of localized defects. Thus, perimetry could effectively capture evidence of afferent visual pathway damage in one or both eyes, for this patient. Furthermore, formal visual field testing may also reveal a subclinical pattern of homonymous vision loss caused by demyelinating lesions in the optic tracts, radiations, or cortex. These subtle defects may be missed with confrontation testing and may also go unnoticed by the patient. Finally, perimetry is essential in this case to help establish or refute the diagnosis of glaucoma. A lack of a current or evolving glaucomatous visual field defect, would cast further doubt on the veracity of this diagnosis.

Third, in the modern ocular imaging era, eye care specialists are no longer restricted to qualitative assessment of the optic nerve, macula, or retinal nerve fiber layer to detect structural damage in the afferent visual pathway. To better characterize this patient's baseline visual status in both eyes, there is information to be gained from using OCT and visual evoked potential testing. The former could help elucidate whether the pattern of retinal nerve fiber layer, macular volume, and ganglion layer loss (in one or both eyes) was more consistent with optic neuritis or glaucoma. Furthermore, visual evoked potential testing could reveal latency delays indicating persistent demyelination or incomplete remyelination. When used in concert with measures of visual function, OCT, and visual evoked potential testing would serve to enhance our understanding of the structural and functional integrity of the afferent visual pathway in this patient.

Is optical coherence tomography necessary to perform?

OCT is not necessary to confirm the diagnosis of remote optic neuritis in an MS patient, which often starts and ends with a good history. Furthermore, the diagnosis of MS in this patient has likely been established on clinical and radiologic grounds. Yet, OCT would help determine what impact MS and glaucoma have had on the afferent visual pathway. In addition, OCT changes over time could be used to capture subclinical aspects of disease activity and progression related to either diagnosis.

During acute optic neuritis, patients manifest peripapillary retinal nerve fiber layer measurements that are either comparable to or increased in their affected eye relative to their fellow eye, whereas intereye differences between macular volume and ganglion layer analysis values are negligible.[8] Retinal nerve fiber layer, macular volume, and ganglion layer analysis values generally decrease for 6 to 12 months after symptom onset, plateauing thereafter. In a meta-analysis of time domain OCT studies (14 studies on a total of 2,063 eyes), retinal nerve fiber layer values were reduced from 5 to 40 μm (averaging 10 to 20 μm) in MS eyes previously affected by optic neuritis.[25] Comparing MS eyes with prior optic neuritis to the eyes of healthy control subjects showed an estimated average retinal nerve fiber layer loss of 20.4 μm (95% confidence interval, −23 to −18). Postoptic neuritis, visual recovery has been associated with the amount of retinal nerve fiber layer, macular volume, or ganglion layer analysis loss observed 6–12 months after the event. In the case presented, OCT values could be compared between eyes to determine the extent of injury caused by prior right optic neuritis, and to ascertain whether values (retinal nerve fiber layer thickness, macular volume, and ganglion layer thickness) are normal or not in the left eye. In reality, the "unaffected" eyes of MS patients are not truly normal. In the aforementioned meta-analysis, 27 time domain OCT studies of MS patients (4199 eyes) showed an estimated retinal nerve fiber layer loss of 14.6 μm (95% confidence interval, −17 to −13) in optic neuritis eyes compared to a 7.1 μm reduction in retinal nerve fiber layer thickness in nonoptic neuritis eyes, relative to control eyes.[25] This observation reflects the fact that clinically silent