Title: “NMOre”: Differentiation of Multiple Sclerosis and Neuromyelitis Optica in New Onset Recurrent Retrobulbar Optic Neuritis.

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Abstract: A male patient suffers unilateral sequential retro bulbar optic neuritis separated by weeks. Clinical and radiologic features are somewhat consistent with the clinical diagnosis of neuromyelitis optica, however, work-up reveals multiple sclerosis is the differentiating etiology.

Case History Patient Visit #1

- Patient Demographics and Chief complaint
  - 40-year-old male Caucasian Veteran that served in the USAF 1997-2007, as a navigator, developed his first case of optic neuritis of the left eye shortly after moving from Texas to Vermont in 2016. He presents to our clinic 31 days after after his first “attack of vision loss” for a second opinion in consultation with neurology.
    - Patient complains that vision and visual field left eye are reduced “just like last time”. Patient reports a deep, throbbing retro bulbar pain OS that seems to worsen on eye movement. Patient denies radiating head pain or a history of migraine. Patient denies other neurological symptoms to include weakness, tremor, loss of coordination or balance, and vertigo.

- Ocular History:
  - Review of prior eye visit to another VA medical center revealed the following exam results:
    - Diagnosis of presumed retro bulbar optic neuritis OS on March 4th 2016.
    - Patient reports blurred vision and visual field left eye and, some shimmering type effect in his vision and pain behind his left eye which was accompanied by a best corrected visual acuity of 20/15 OD and 20/25 OS.
    - EOM’s were notable for smooth accurate pursuits, saccades with full excursions and no pain OU.
    - No APD OU
    - Normal Ishihara color vision OU
    - Red Cap Desaturation was negative, but notable for a “haze of glare” which was noticed when the cap was observed with the left eye.
    - Anterior segment and posterior segment findings were normal and optic nerve pallor was specifically noted as being absent OU.
    - Visual field testing (24-2 HVF) was ordered that day had overall reliable results.
    - The mean deviation OD was -1.14dB and no defects were revealed.
    - The mean deviation OS was -20.54 and dense absolute altitudinal defects were seen both superior and inferior hemispheres up to midline inferior and superior.
    - OCT of both eyes revealed no edema or thickening of either macula or optic nerves.
    - Diagnosis at that time was presumed retrobulbar optic neuritis OS with a plan to follow up one month. No steroids or other treatments were instituted at that time according to the notes. Patient was referred to neurology to rule out multiple sclerosis.
Medical history
- Medical history is significant for HTN, morbid obesity, hypertriglyceridemia, obstructive sleep apnea, nephrolithiasis, depression, and Type 2 Diabetes Mellitus for ten years.

Medications include allopurinol, gemfibrozil, glipizide, hydrochlorothiazide, lisinopril, and metformin, allopurinol, gemfibrozil, glipizide, hydrochlorothiazide, lisinopril, and metformin.

Examination Findings:
- Visual Acuity OD: 20/10 and OS 20/200
- 2-3+ APD was noted OS.
- OCT that day was consistent with previous imaging and revealed no thickening or thinning of the retinal nerve fiber layer OU
- The Humphrey Visual Field 24-2 was reliable. No visual field defects were noted right eye. The left eye revealed an overall depression of MD OS with diffuse relative loss of the entire visual field
- Anterior segment findings and IOP were normal
- Posterior segment findings were normal to include intact optic nerves devoid of edema or pallor OU.
- Working diagnosis was multiple sclerosis related retrobulbar optic neuritis versus neuromyelitis optica.
- Patient was offered I.V. methylprednisone treatment along with appropriate education which included the risks and benefits of this treatment. Education included a description of short term recovery versus long term outcomes. Other steroid side effects were described, to include the potential for intermittent elevated blood glucose. The patient decided that he would like to forego steroid treatment given overall risks and benefits presented to him.
- MRI results were available at this visit and results were reviewed in consultation with neurology. Case discussion resulted in expanding the differential to include neuromyelitis optica due to the temporal recurrence and severity of optic neuritis as well as the location of demyelinating lesions seen on MRI.
- Vitamin D levels and antibodies to aquaporin-4 (AQP4-Ab or NMO-IgG) were ordered by Optometry and neurology ordered additional laboratory testing to further rule out other causes of optic neuritis or demyelinating lesions to include Lyme, syphilis, Lupus, and sarcoid. Plan was to return in one month as long as no new neurological or visual symptoms arose.

Case History Patient Visit #2
- Patient presents 28 days after his initial exam, noted above, reporting complete resolution of his vision and visual field OS. Patient continued to deny any other prior episodes of vision loss. He also denies other neurological symptoms to include headache, weakness, tremor, loss of coordination or balance, vertigo now or at any other time in his life.
  - His retrobulbar pain OS entirely resolved
  - Visual acuity was: OD: 20/10 OS: 20/10
  - APD was absent to trace OS
Anterior and posterior segment findings were normal and optic nerves were notably devoid of pallor or edema OU.
- OCT was symmetric and revealed no thickening or thinning of either optic nerve.
- Humphrey visual field 24-2 threshold testing revealed normal modal values and no defects OU.

- Plan was to follow up with neurology and review laboratory and radiological findings as they became available. Patient was educated to RTC with any new visual or neurological symptoms. Patient was offered a number of treatment options for multiple sclerosis by neurology but as of the writing of this case patient continued to refuse all treatments.

- Radiology studies:
  - MRI of the brain and cervical spine with gadolinium revealed “increased intermediate signal intensity of in the left optic nerve without definite enhancement or swelling consistent with clinical history of optic (retrobulbar) neuritis.” Fifteen non-enhancing FLAIR lesions were found in the periventricular and supratentorial periventricular white matter. With an enhancement oriented perpendicular to the right lateral ventricle, the presence of a ‘Dawson’s finger’ was questioned. Upon imaging the cervical and thoracic spine both with and without contrast, 2-4 lesions were observed in the cervical and thoracic spinal cord. Of note, a lesion at C5,6 was found to have an ill-defined enhancement. Additional lesions of the upper thoracic cord and possibly medulla were all consistent with demyelination.

- Laboratory Findings: Lyme, systemic lupus, syphilis, and sarcoid were all ruled out through laboratory testing
  - Both Lyme antibody and ANA were negative, respectively ruling out Lyme’s Disease and Systemic Lupus Erythematosus.
  - RPR was non-reactive, ruling out syphilis.
  - Sarcoid was ruled out with an Angiotensin-1 converting enzyme (ACE) was found to be 17 units.
  - Vitamin B12 was found to be on the very low end of normal at 237 pg/mL.
  - Vitamin D was found to be 15.5 ng/dL
  - Antibodies to aquaporin-4 (AQP4-Ab or NMO-IgG) was negative.

Differential diagnosis
- Primary/leading
  - Retrobulbar optic neuritis due to multiple sclerosis
  - Neuromyelitis optica
- Other differentials
  - Sarcoid crisis, asymmetric thyroid ophthalmopathy, migraine, and idiopathic optic neuritis
Diagnosis and Discussion

Reduction in acuity, pain on eye movement, the presence of an Afferent Pupillary Defect (APD), and the absence of pathology on ophthalmoscopy are hallmark signs of acute retrobulbar optic neuritis. The differential for optic neuritis is broad and in many cases idiopathic, however, MRI, clinical, and laboratory findings in this case helped narrow the differential to multiple sclerosis (MS) associated optic neuritis and neuromyelitis optica (NMO). These conditions were once thought to be on a shared spectrum, however, ongoing research indicates that diagnostic, treatment, and prognosis criterion for each condition are different. Hallmark clinical signs of NMO are optic neuritis, longitudinally extensive transverse cervical myelitis, and a positive aquaporin-4 antibody (AQP4 antibody). The demyelinating inflammatory lesions of the optic nerve often found in NMO can be more visually devastating and longer lasting than the optic neuritis associated with MS. MS associated sequential recurrence of optic neuritis, as seen in our case, has not been identified as a unique clinical feature. Contrarily, multiple-sclerosis related optic neuritis can present with optic neuritis and a variety of other concurrent symptoms and MRI lesions. In our case, the patient initially presented with new onset of sequentially recurrent optic neuritis with severe vision and visual field loss, cervical enhancing demyelinating lesions, and the absence of other neurological symptoms. This presentation is somewhat more clinically common in NMO, particularly in patients who were otherwise previously asymptomatic. Demyelinating lesions were found in the paraventricular spaces which is common for multiple sclerosis, however, the number of cervical enhancing lesions were just shy in number and transverse quality for NMO diagnostic criterion. Further, NMO patients often present without demyelinating brain lesions and our patient had several as mentioned herein. The overall clinical presentation and a negative AQP4 resulted in a final diagnosis of multiple sclerosis. Moreover, Multiple Sclerosis (MS) is a more common demyelinating disease in which lesions discovered on MRI are found to be patchier in appearance and rarely extend beyond 2-3 vertebral lengths which was not seen in our case.

Neuromyelitis Optica (NMO), also known as Devic’s disease, affects between 0.52/10^5 and 4.4/10^5 people, making it a fairly rare but potentially devastating disease. NMO is a humoral immune system mediated demyelination of both grey and white matter. Although largely driven by NMO-IgG antibody against AQP4 (aquaporin 4) of the astrocytes, diagnostic criteria for NMO published in 2015 also allows for AQP4 negative patients to be diagnosed with NMO. NMO will typically present as a relapsing course of optic neuritis, transverse myelitis, or both. Assuming other diagnoses have been ruled out, MRI findings are currently only necessary for a diagnosis of AQP4 negative cases. MRI lesions within NMO typically span ≥3 segments of the spinal cord and are more centrally located in the spinal cord compared to MS lesions. Additionally, lesions may present as “cloud like” in appearance. Chronic cord lesions in NMO often change over time, becoming patchier in appearance, making these distinguishing criteria less applicable to older lesions. NMO is much more common in women, representing 2/3 of cases making it less likely for our patient to be affected by this disease regardless of other clinical findings. However, relying on epidemiology in this case was not particularly helpful.

OCT did not reveal optic nerve thinning at any point in the post-inflammatory period in our patient case. OCT biomarkers have been proposed as a potential biomarker for differentiating MS and NMO by Naismith et al. In their study, there was thinner nerve fiber layer findings overall and in the inferior and superior quadrants compared to MS associated optic neuritis. Our patient did not have any relative nerve fiber thinning rendering this marker unhelpful in our case.
Treatment, management

Differentiating MS associated optic neuritis from neuromyelitis optic is important for the selection of the best treatment. NMO is an aquaporin-4 autoimmunity and complement-mediated injury disease so drug targets are focused on suppressing this activity. Therefore, plasmapheresis and other immunotherapies such as methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, and rituximab are used to treat patients with NMO. Methylprednisone has been used to prevent recurrence, however, there is emerging evidence that this may exacerbate this condition. MS-associated optic neuritis treatment continues to be I.V. methylprednisone for acute presentation with supportive long term therapies for the underlying multiple sclerosis such as, fingolimod (Gilenya), dimethylfumarate (Tecfidera), and teriflunomide (Aubagio), laquinimod; daclizumab, ocrelizumab, and alemtuzumab.

Finally, holistic supportive therapies such as correction of Vitamin D deficiency have been studied in patients with multiple sclerosis, however, most studies fail to show that Vitamin D can reverse MRI associated lesions. However, these studies do not show harm from Vitamin D supplementation and there is good evidence that Vitamin D may play a role in prevention and modulation of MS and Type II diabetes. This patient’s low Vitamin D was treated because there is good evidence that it may be supportive of his other health conditions to include Type II diabetes and lower levels of Vitamin D have been repeatedly associated with increased risk of MS relapse.

Conclusion

Multiple sclerosis associated optic neuritis and neuromyelitis optic have similar clinical findings, however research has revealed helpful diagnostic criterion for differentiating these two conditions. Treatment, management, and prognosis of these conditions are not the same, so differentiation is important in clinical decision making and patient education of expected disease course.
References