

4 QUESTION

HOW SHOULD I EVALUATE AND MANAGE SUSPECTED OPTIC NEURITIS?



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A 25-year-old woman reports sudden loss of vision OD, pain with eye movement, a right relative afferent pupillary defect, and a normal fundus examination. Right optic neuritis is suspected. What would you recommend for a work-up?

The first step is to firmly establish the diagnosis; you have done most of the clinical work already in that you mention the existence of an afferent pupillary defect and normal fundus. I would certainly want to know the visual acuity, color vision, and visual field for follow-up purposes, but everything you have mentioned thus far points to a retrobulbar optic neuropathy. Together with the history, I agree with you that this is quite consistent with retrobulbar optic neuritis. In particular, periorbital pain is very common (92% in the Optic Neuritis Treatment Trial [ONTT]), and a history of pain with eye movements is often elicited. Despite the fact that this sounds archetypal for retrobulbar optic neuritis, it is worth keeping in mind the possibility of other retrobulbar optic neuropathies if the subsequent clinical course mandates. Nevertheless, we do not order routine labs as part of the initial work-up in such patients.

Working on your diagnosis of retrobulbar optic neuritis, management requires magnetic resonance imaging (MRI), then we need to make an acute therapeutic decision (the use of steroids) followed by a chronic therapeutic decision (consideration of multiple sclerosis [MS] immunomodulatory therapy). I typically order an MRI of brain and orbits with and without contrast (Figures 4-1 and 4-2); the orbital portion helps rule out structural mimics and assists in confirmation (the optic nerve typically enhances if the scan is obtained within the first 3 to 4 weeks). You should be aware that gadolinium-based contrast agents used in MRI may be associated with a progressive fibrosing disease

Figure 4-1. Axial fluid-attenuation inversion recovery (FLAIR) MR study shows periventricular multifocal hyperintense white matter lesions consistent with demyelination.

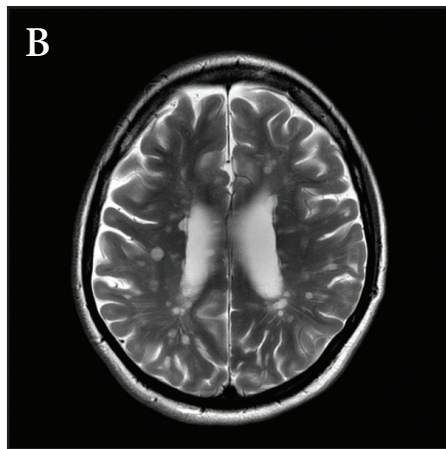
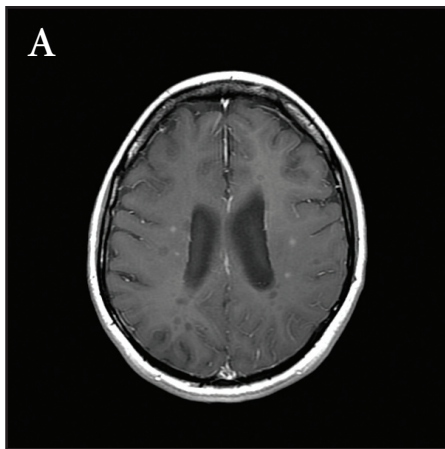
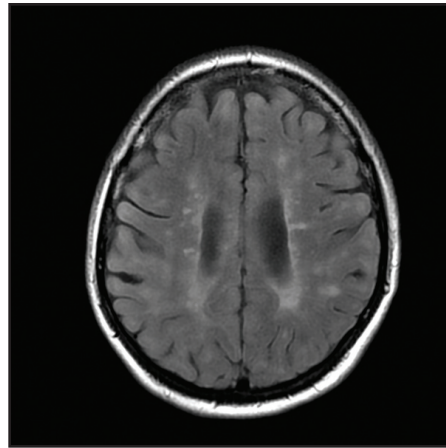


Figure 4-2. (A) Axial T1-weighted MRI post-gadolinium demonstrates enhancing white matter lesions bilaterally. (B) Axial T2-weighted MRI shows periventricular multifocal hyperintense white matter lesions consistent with demyelination.

(nephrogenic systemic fibrosis) in patients with renal failure; additional contraindications to gadolinium contrast include known allergy to the agent or pregnancy. In my opinion, a lumbar puncture is not necessary in the majority of typical optic neuritis cases, although the presence of unique spinal fluid oligoclonal bands may be an independent risk factor for the development of MS, especially if the initial MRI is normal.

The ONTT and its follow-up study, the Longitudinal Optic Neuritis Study (LONS), provide the evidence base for the prognosis of optic neuritis and the use of steroids, and provide data pertaining to the risk of subsequent MS development. The ONTT-randomized patients with acute optic neuritis (<8 days duration) to intravenous (IV) methylprednisolone (250 mg every 6 hours for 3 days followed by a prednisone taper), oral prednisone (1 mg/kg), or placebo. Regardless of treatment group, the prognosis for visual recovery after optic neuritis is generally quite good, with 95% of patients achieving Snellen acuity of 20/40 or better at 12 months; however, the oral prednisone in 1 mg/kg dose in the ONTT was associated with twice the risk of recurrent optic neuritis and is therefore contraindicated. Accordingly, our therapeutic decision involves high-dose

methylprednisolone or no steroid therapy. High-dose steroids in the ONTT were associated with a more rapid recovery of visual function, may provide partial protection against the development of MS over the subsequent 2 to 3 years only, and often resolve pain issues rapidly. The potential side effects of steroids are well known and include hyperglycemia, gastrointestinal symptoms, mood alteration (including rare psychosis), insomnia, and the infrequent occurrence of avascular necrosis. Keeping in mind that high-dose steroids merely alter the rate of recovery (not the ultimate extent of recovery), I typically will discuss the risk, benefits, side effects, and alternatives with each patient in light of his or her unique medical history and individual preferences. I tend to offer high-dose methylprednisolone (1 g IV every day for 3 days followed by oral prednisone 1 mg/kg every day for 11 days followed by a 4-day taper) to most patients unless there is a contraindication or patient preference dictates otherwise.

Optic neuritis has a well-known association with MS and is a common first symptom of the disease. The brain portion of the MRI is essential to stratify this patient's risk of subsequent MS and is a key factor in the chronic therapeutic decision we need to make regarding immunomodulatory therapy. The LONS demonstrated that a normal MRI is associated with a 5-year MS risk of 16%, while an abnormal MRI (at least 3 T2 hyperintensities typical of demyelination) corresponds to a 5-year MS risk of 51% (see Figures 4-1 and 4-2). At 10 years, a normal MRI is associated with an MS risk of 22%, while any T2 lesion corresponds to an MS risk of 56%. At 15 years, a normal MRI is associated with an MS risk of 25%, while any T2 abnormality translates to an MS risk of 72%. A normal MRI in combination with certain clinical characteristics also defines a very low MS risk cohort; anterior optic neuritis (ie, papillitis) in a male with a normal MRI is associated with a very low MS risk (only 4% at 15 years). Additionally, with a normal MRI, severe disc edema, disc hemorrhage, painless onset, the presence of a macular star figure, or no light perception visual acuity at onset are features that define a cohort that did not convert to MS even after 15 year follow up.

Trials using interferon beta-1a, interferon beta-1b, or glatiramer acetate in clinically isolated syndrome patients at high risk for MS development have all reported significantly delayed disease progression when these agents are given early (CHAMPS, BENEFIT, and PreCISe trials). The CHAMPS trial randomized patients after a first demyelinating event typical of MS and an MRI with at least 2 T2 lesions to either weekly interferon beta-1a IM or placebo, and approximately 50% of the subjects entered the trial with optic neuritis as their initial demyelinating event. Subjects randomized to interferon beta-1a had a significantly lower conversion rate (42% decreased) to MS compared to subjects on placebo. Very similar findings have since been shown for interferon beta-1b SC qod, and glatiramer acetate.

Summary

- * A patient presenting with optic neuritis requires an evaluation that includes clinical history and exam; a targeted MRI scan; and discussion concerning the risk, benefits, side effects, and alternative regarding a treatment course with high-dose steroids.
- * In appropriate patients with high-MS risk MRI findings, referral to an MS expert or a similar discussion concerning institution of anti-MS immunomodulatory therapy such as interferons is important for long-term neurologic health.

Bibliography

- CHAMPS Study Group. Interferon β -1a for optic neuritis patients at high risk for multiple sclerosis. *Am J Ophthalmol.* 2001;132:463-471.
- Jacobs LD, Beck RW, Simon JH, et al (CHAMPS Study Group). Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med.* 2000;343:898-904.
- Kaufman DI, Trobe JD, Eggenberger ER, Whitaker JN. Practice parameters: the role of corticosteroids in the management of acute monosymptomatic optic neuritis. *Neurology.* 2000;54:2039-2044.
- Optic Neuritis Study Group. The 5-year risk of MS after optic neuritis: experience of the Optic Neuritis Treatment Trial. *Neurology.* 1997;49:1404-1413.
- Optic Neuritis Study Group. The clinical profile of acute optic neuritis: experience of the Optic Neuritis Treatment Trial. *Arch Ophthalmol.* 1991;109:1673-1678.

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QUESTION

WHAT DO I TELL MY PATIENTS WITH OCULAR MYASTHENIA ABOUT THEIR CHANCES OF IT PROGRESSING TO THE REST OF THEIR BODY? DO I NEED A NEUROLOGIST?



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The patient is a 45-year-old man with proven ocular myasthenia gravis (OMG). What are his chances of developing generalized myasthenia gravis (GMG)? How likely do you think it is for a patient with OMG to develop generalized symptoms and what problems could occur? Are there other medicines he should avoid?

The majority of patients with myasthenia will present with the ocular findings and the odds are that 20% to 40% of patients will remain ocular. If their disease persists as ocular for 2 years, then 90% will not further generalize. The remaining 60% to 80% of patients who do not remain ocular might require therapeutic medical and/or surgical intervention but today can generally expect an excellent outcome. However, there are 4 outcome modifiers for the GMG group: 1) rapid progression of systemic weakness, 2) severely impaired respiratory function, 3) thymoma, and 4) autoimmune disease. For these reasons we do believe that ophthalmologists should consult a colleague in neurology or neuro-ophthalmology for their OMG patients.

The consulting neurologist or neuro-ophthalmologist might consider a number of additional tests for the evaluation of pernicious anemia: antinuclear antibody (ANA), rheumatoid factor, myasthenia antibody panel, anti-MuSK antibodies, Tensilon or Prostigmin test; renal function: computed contrast tomography of the chest (eg, thymoma

or thymic hyperplasia); thyroid function tests; pulmonary function tests; or repetitive electromyography stimulation (particularly single fiber).

About 10% of ocular myasthenia patients will experience a spontaneous remission. The patient with pure ocular involvement has options unless there is thymoma or autoimmune disease involvement, since these will require direct intervention. To some degree, the intervention is balanced by the degree of ocular involvement, age, comorbidity, and lifestyle. A patient with minimal involvement can be observed, while disease progression with accompanying lifestyle impact is assessed, because symptomatic ocular progression usually happens within the first 3 to 4 years of the disease.

Anticholinesterase agents are most effective for fatiguing ptosis. While the usual starting dose of pyridostigmine is 60 mg 3 times daily, each dose is metabolized completely in 4 hours. Hence, a starting dose that ensures a more even titration may be achieved by 30 mg every 3 hours (5 to 6 doses) while awake (a pre-nap or bedtime dose is not necessary). Subsequent titration depends upon patient response, which can be assessed by a patient diary and outpatient visits in the afternoon. Systemic effects are usually gastric distress and diarrhea, which can be handled with reassurance and specific therapy; muscle cramps may occur but are neither severe nor ominous. Oral atropine can ameliorate some side effects but it is usually not necessary at standard doses for OMG. Since the extraocular muscle(s) involvement can be variable and asymmetric, it is more difficult to treat diplopia effectively with pyridostigmine. Assistive devices such as Fresnel prisms will be helpful if the extraocular muscle involvement is minimal and stable; lid crutches for ptosis usually are not tolerated.

It has been my practice to perform skin testing for latent tuberculosis at the initiation of steroid treatment, but this is not a universal recommendation. In addition, high-dose steroids can produce a paradoxical severe weakness and respiratory collapse so it has been preferred to introduce steroids slowly at the rate of 10 to 20 mg daily (or on alternate days in mild cases). This is increased by 5 to 10 mg daily every 5 to 7 days until clinical improvement or a dose of 60 mg occurs. It is certainly important to alert the patient of concerns for additional or sudden weakness, but most tolerate this slower induction well. Hand-held plastic tidal volume measures (such as are used at home by asthmatics) are optional but not essential. When the patient is stable for at least 3 months, the dose can be gradually reduced in 5-mg increments to a low maintenance dose of 7.5 to 12.5 mg daily or alternate day dosing of 10 to 15 mg. Clinical responses usually are apparent within 2 to 4 weeks with maximum benefit occurring by 6 to 12 months. If symptoms recur, then the dose can be increased by 10- to 20-mg increments each week until the patient is clinically improved again.

Corticosteroid use becomes an important consideration due to potential life-threatening problems such as respiratory impairment, which occurs with GMG. Dysphagia bulbi especially for liquids is an alerting sign of bulbar and potential respiratory involvement; solids and semi-solids may descend more easily through the esophagus with less muscle coordination required. Early treatment with corticosteroids might reduce the rate of progression to GMG although this still remains a bit controversial. Studies where treatment was started more than 1 year after disease presentation have shown less clear results. Subsequent exacerbations may occur despite any therapy and require retreatment in many patients until their therapy has been individualized successfully.

The risks of steroids include Cushing-like changes, diabetes mellitus, hypertension, gastric ulceration, proximal muscle weakness, infections, cataracts, and osteoporosis. The patient and his or her primary care physician can help monitor blood pressure, diet control, and physical therapy for proximal muscles. Osteoporosis and gastric mucosal changes can be anticipated and patients treated during steroid therapy. Dosing must be slowly tapered to alternate days to minimize the risk of adrenal insufficiency. However, in OMG patients in whom steroids were ineffective or cannot be used, other agents such as azathioprine and mycophenolate mofetil have been well-tolerated and effective; thymectomy has also had favorable results in some OMG studies. Cyclosporine as an immunostatic anti-T-cell agent has such renal and hepatic effects that it is only used as later and alternative treatment. Intravenous immunoglobulin has been helpful in juvenile MG or in GMG where steroids have not been tolerated.

The list of drugs or agents that could be *avoided if possible* in myasthenia patients is long. It includes the statins and possibly gabapentin, which may uncover latent myasthenia, as well as D-penicillamine, which induces MG. It also includes all the “-mycin” antibiotics, aminoglycosides, tetracycline, ciprofloxacin, bacitracin, beta-blockers (including topical), calcium channel-blockers, quinine, anti-arrhythmias, lithium, chloroquine, respiratory depressants, magnesium sulfate, and neuromuscular blockers.

Summary

- * OMG should probably be managed by an ophthalmologist in conjunction with a neurologist or neuro-ophthalmologist.
- * Generalization of OMG to systemic MG is common but typically occurs in the first 2 years following the diagnosis of OMG.
- * Corticosteroids might reduce the rate of generalization of OMG but remains controversial.

Bibliography

- Chavis PS, Stickler DE, Walker A. Immunosuppressive or surgical treatment for ocular myasthenia gravis. *Arch Neurol.* 2007;64:1792-1794.
- Gilbert ME, De Sousa EA, Savino PJ. Ocular myasthenia gravis treatment: the case against prednisone treatment. *Arch Neurol.* 2007;64:1790-1792.
- Grob D. The course of MG and therapies affecting outcome. *Ann N Y Acad Sci.* 1987;505:472-499.
- Kupersmith MJ, Latkany R, Homel P. Development of generalized disease at 2 years in patients with ocular myasthenia. *Arch Neurol.* 2003;60:243-248.

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QUESTION

HOW DO I MANAGE HEADACHE SYNDROMES THAT COME TO ME AS AN OPHTHALMOLOGIST?



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A 37-year-old woman who has developed recurrent left-side headaches over the past 2 months is being examined. The pains are located in the left orbital-temporal region, are excruciatingly severe, last 4 to 10 minutes, occur 8 to 15 times per day, and are associated with bilateral conjunctival injection and lacrimation. The neuro-ophthalmologic exam was normal. What entities should be considered as a cause of these paroxysms? What treatments should be considered?

The patient who complains about headache to an ophthalmologist usually wonders if the pain has to do with the eye. A long-lasting (hours-days) unilateral headache that is moderate to severe and associated with nausea and/or vomiting as well as photophobia is usually migraine. However, a short-lasting headache in and around the eye or head with autonomic symptoms can be a vexing problem for any ophthalmologist. The good news is that short-lasting headaches can be diagnosed and treated.

The first problem is recognition that stabbing pains are a “primary headache disorder” and not due to a secondary process. The patient understandably believes that the severe pain occurring in the orbital temporal region is due to a serious problem like a tumor or an aneurysm. Headaches that are due to an underlying process by definition must be excluded. I use the following “rules of thumb” to help me diagnose a secondary headache:

- * A new headache in someone who is not otherwise headache prone
- * A headache in an older person—always rule out giant cell arteritis
- * A side-locked headache that never goes away—needs imaging

- * A headache associated with neurological findings: Horner syndrome (rule out carotid dissection), weakness, numbness, diplopia
- * A headache that awakens someone in the middle of the night provided it is not a cluster or other trigeminal autonomic cephalgia
- * Eye diseases that could present with episodic eye pain include glaucoma and trochleitis (usually find tenderness over the trochlea). Other eye disorders like early Zoster ophthalmicus, optic neuritis, and posterior scleritis will not have episodic eye pain but may have pain as the presenting symptom

In many of the stabbing headache syndromes, imaging studies may have been performed before you see the patient. If not, or you are in doubt, consider ordering magnetic resonance imaging (MRI) for these short stabbing headaches to be sure there is no abnormality in the pituitary gland, cavernous sinus, or skull base.

Fortunately, most recurrent stabbing or throbbing pains are primary headache disorders. The next job is to diagnose the headache type. The clues to look for are symptoms of autonomic dysfunction: ptosis, eyelid edema, lacrimation, rhinorrhea, red eye, possibly an intermittent Horner syndrome (with ptosis, miosis), and conjunctival injection. If the patient has any one of these symptoms along with episodic unilateral pain in and around the eye, chances are the patient has a primary short-lasting headache or "trigeminal autonomic cephalgia." The patient above has conjunctival injection and lacrimation.

Next determine which type of trigeminal autonomic cephalgia the patient has. These headaches divide themselves between the length of the headache, the number of headaches each day, and the gender of the person. In general, cluster headache and short unilateral neuralgiform pain with conjunctival injection and tearing (SUNCT) are more common in men, whereas paroxysmal hemicrania and hemicrania continua are more common in women.

The length of time of the pain is helpful. The longest trigeminal autonomic cephalgia is hemicrania continua. It is characterized by chronic pain on one side of the head with paroxysms of stabbing pain on top of that. The pain can last hours or days. The next longest is cluster headache lasting 20 to 120 minutes. Paroxysmal hemicrania is much shorter, usually 2 to 45 minutes at a time. Short unilateral neuralgiform pain with (SUNCT) or without (SUNA) conjunctival injection and tearing are 15 to 120 seconds each.

Hemicrania continua is by definition continuous. Cluster occurs anywhere between 1 to 3 times each day; most of the time, one of the pains will occur in sleep. Paroxysmal hemicrania occurs usually more than 5 times each day. SUNCT/SUNA can occur 30 times an hour.

Using Table 28-1, we have a woman with 8 to 15 attacks a day lasting 4 to 10 minutes each; this fits with paroxysmal hemicrania.

Preventative treatment with indomethacin is always worth a try in many of these short-lasting headaches. Hemicrania continua and paroxysmal hemicrania have the absolute response to this medication as part of the definition of the headache. Doses of 25 mg 3 times each day to 75 mg slow release form twice each day usually suffice. When indomethacin is not tolerated or can not be used, Cox-2 inhibitors, verapamil, aspirin, and anticonvulsants (gabapentin, topiramate, valproate, lamotrigine) may be used.

Acute treatment of the pain is difficult. Most of the time the headache is so brief that acute treatments will not be helpful. Oxygen can be administered at the onset of the headache (cluster headache usually responds to oxygen 5-10 L/minute for 10 min) may be

Table 28-1

Distinguishing Trigeminal Autonomic Cephalgias

<i>Headache Type</i>	<i>Gender</i>	<i>Length of Headache</i>	<i>Frequency</i>	<i>Response to Indomethacin</i>
Hemicrania continua	Female>male	Continuous	Multiple stabbing pains on top of continuous headache	Complete
Paroxysmal hemicrania	Female>male	4 to 15 minutes	>5 day; nocturnal headache	Complete
Cluster headache	Male>female	30 to 120 minutes	1 to 5/day; often nocturnal onset	Rarely helpful
SUNCT	Male>female	5 to 250 seconds	1/day to 30/hour	Rarely helpful
SUNA	Male>female	5 to 250 seconds	1/day to 30/hour	Rarely helpful

helpful. Also in cluster headache because it lasts longer, trials of intranasal triptans such as sumatriptan, zolmitriptan, or injectable sumatriptan may be useful.

Your patient probably has paroxysmal hemicrania. She probably will need to be referred to a neurologist to try specific medication treatments for this entity.

Summary

- * Although most recurrent stabbing or throbbing headaches are primary headache disorders, always consider secondary headache or eye pain syndromes.
- * In many of the stabbing headache syndromes, imaging studies may have been performed before you see the patient. If not, or you are in doubt, order an MRI for these short stabbing headaches to be sure there is no abnormality in the pituitary gland, cavernous sinus, or skull base.
- * It is important to look for symptoms of autonomic dysfunction in patients with unilateral headache or eye pain. These symptoms include ptosis, eyelid edema, lacrimation, rhinorrhea, red eye, possibly an intermittent Horner's syndrome (with ptosis, miosis), and conjunctival injection. If the patient has any one of these symptoms along with episodic unilateral pain in and around the eye, chances are the patient has a primary short-lasting headache or trigeminal autonomic cephalgia.
- * Trigeminal autonomic cephalgias are defined by the length of the headache, the number of headaches each day, and the gender of the person.

Bibliography

- Cohen AS, Matharu MS, Goadsby PJ. Trigeminal autonomic cephalgias: current and future treatments. *Headache*. 2007;47:969-980.
- Favier I, van Vliet JA, Roon KI, et al. Trigeminal autonomic cephalgias due to structural lesions: a review of 31 cases. *Arch Neurol*. 2007;64:25-31.
- Friedman DI. The eye and headache. *Ophthalmol Clin North Am*. 2004;17:357-369.
- May A. Update on the diagnosis and management of trigemino-autonomic headaches. *J Neurol*. 2006;253:1525-1532.