high and pathological myopia in teenagers and young adults should not be overlooked. New evolving technologies for the early diagnosis, medical, and surgical treatment of specific myopia related pathologies, such as laser photocoagulation for choroidal neovascularisation, will improve the prognosis of patients at risks of severe visually incapacitating complications. If the risks of pathological myopia are proportional to the severity of myopia, measures to prevent the early onset and rapid progression of myopia in childhood will eliminate or reduce pathological myopia later in life.

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Optic neuritis

The approach to bilateral simultaneous isolated optic neuritis

L Frohman

These patients require keen attention from the first ophthalmologist to contact them

In this issue of *BJO* (p 551), de la Cruz and Kupersmith describe a series of 15 adult patients who presented to a neuro-ophthalmic referral practice over a 5 year period with bilateral simultaneous optic neuritis. Patients were not included in this series if they had either evidence of multiple sclerosis or myelopathy, a known systemic disease or medication that is associated with optic neuropathy, or cancer. They were evaluated for systemic disease by a battery of testing including lumbar puncture, which was abnormal in two patients. They indicate that in one case, their patient was ultimately shown to have sarcoidosis, the others did not have a specific diagnosis made (although three (20%) were thought to be post-viral). Their data show that most of these cases have a good outcome when treated with their recommended corticosteroid regimen of 3–5 days of intravenous methylprednisolone 1 g daily followed by a taper of oral prednisone tailored to the clinical course.

Fortunately, the presentation with bilateral simultaneous optic neuritis in adults is unusual, yet because of the devastating implications for the patient, possibly including occult yet active systemic disease, these patients require keen attention from the first ophthalmologist to contact them.

The key to applying the data in this paper to a patient you might encounter is to know if the entry criteria apply

The key to applying the data in this paper to a patient you might encounter is to know if the entry criteria apply. Certainly, a history and examination to rule out occult demyelinating disease is a given, and if a drug that causes optic neuropathy is being used, it will immediately be a suspect cause. If the patient has a known neoplasm, then one will carefully search for a process such as carcinomatosis, which could affect each

optic nerve, or for a metastasis that involves the chiasm. But the protocol proposed by de la Cruz and Kupersmith does not apply if the patient has a known systemic disease. Thus, a major issue is just how far does one go in such a patient to search for an occult underlying process that could cause bilateral optic neuropathy because, if it were found, not only would the lessons of this series not apply, but the systemic process might require urgent specific therapy.

One should first take a detailed history looking for undiagnosed chronic systemic disease or a recent systemic illness or heraldic event. In a patient who had received a vaccination 2 weeks earlier, one will strongly consider post-vaccinal optic neuritis. If there was a significant viral syndrome just before onset, one will consider post-viral optic neuritis. We also typically inquire about symptoms that would be consistent with collagen-vascular disease, vasculitis, or occult infection (for example, lues) or inflammations (for example, sarcoidosis). Thus, we ask about symptoms such as arthralgia, myalgia, haematuria, haemoptysis, chronic fevers, rashes, parotid/facial swelling, mucosal ulcerations. As an example, the presence of asthma or chronic cough of relatively recent onset makes us think of processes such as sarcoid, vasculitis, or tuberculosis. Mucosal membrane ulceration makes us think of infections such as syphilis or Behçet's disease. Recurrent thrombosis or early fetal wasting make us consider anti-phospholipid antibody syndrome.

As one obtains a history that helps focus a differential diagnosis, one moves to a directed physical examination looking for findings that would support specific entities. Was there something about the disc that might be a clue? Although Leber's optic neuropathy does not typically present with simultaneous onset, one eye might not have been noted by the patient, so the second eye's ictus might be perceived as sudden bilateral visual loss. Are there the typical telangiectasia seen on the disc that might make one obtain mitochondrial gene analysis?

Furthermore, in a patient with bilateral optic neuritis, we would always look for evidence of uveitis, past or present. This series excluded patients with uveitis. There is no question of aetiopathogenic and clinical links between multiple sclerosis and uveitis. Although multiple sclerosis is seen in patients with uveitis at an incidence of about 1%, and uveitis seen in patients with multiple sclerosis at about the same frequency,^{1,2} the exact incidence of uveitis in patients with optic neuritis without multiple sclerosis is not clear. I think that the presence of uveitis with bilateral simultaneous optic neuritis strongly argues the presence of a systemic process and should never be attributed to the optic neuritis-multiple sclerosis disease complex without further investigation. We carefully look for iris or conjunctival nodules and look at the lacrimal glands. We search the retina and choroid for granulomas, and look for periphlebitis. If we find either a history or sign that supports undiagnosed systemic disease, we either begin a directed examination ourselves, or enlist an internist with experience in such processes—for example, a rheumatologist, or clinical immunologist. As an example, if we find uveitis or lacrimal gland swelling in this setting, we strongly consider sarcoidosis, and have found that a gallium or PET scan is useful for revealing occult sites of disease activity that might be biopsied for histological confirmation.^{3,4}

We would agree with this paper's treatment regimen, and its rapid initiation after the diagnostic evaluation is expediently obtained. If one finds nothing in the history or examination that suggests that the bilateral optic neuritis is but an iceberg heralding what is deeper, then one has two options after initiating therapy as suggested by the authors. The diseases that can be missed at this point and that have major implications for the patient's vision and overall health include:

- truly occult systemic disease
- paraneoplastic disease

- autoimmune visual disease (for example, autoimmune related retinopathy⁵ and optic neuropathy (ARRONS), or autoimmune optic neuropathy⁶)
- autoimmune neurological disease associated with optic neuritis (for example, neuromyelitis optica⁷).

Generally, what one can do at this point is to carefully follow the clinical course. If the patient has a truly isolated bilateral optic neuritis as are the cases in the current series, then, after several weeks, one expects to see improvement. If there is either no improvement, or there is worsening or rebound with steroid withdrawal, then one can go to a second stage of diagnostic evaluation, which might include looking for the above entities. Obviously, if systemic symptoms manifest as the patient is being carefully followed, then one again evaluates for undiagnosed systemic disease.

At this point, if there is no obvious disc pallor, especially if there are central scotomas and no pain, then one might entertain obtaining electrophysiology to determine if the visual loss could actually be of photoreceptor origin (for example, fundus negative cone dystrophy). This is especially important if there are significant photopsias or shimmering reported by the patient, as these are more typical of a retinal process. Making this determination is critical, as one of the next steps is to look for paraneoplastic or autoimmune causes of visual loss, and knowing if the visual loss is optic nerve or retinal in origin will help one select what assays to obtain. If the process were a rod process, one might start with looking for the 23 kDa cancer associated retinal antigen (anti-recoverin⁸). If one knew it was definitely an optic nerve process, one might consider sending serum to be tested for evidence of autoimmune neurological disease (that is, anti-NMO⁷) or for paraneoplastic optic neuropathy markers such as anti-CRMP5,⁹ or obtain serological markers such as antinuclear antibody and anticardiolipin antibody, and perhaps a skin biopsy, looking for autoimmune optic neuropathy.⁶

In the patient who does have isolated monophasic bilateral simultaneous optic neuritis, we need to consider if this is truly as unusual as we might think. The Optic Neuritis Treatment Trial (ONTT) showed that 48% of patients with unilateral optic neuritis had contralateral field defects on automated perimetry at onset.¹⁰ Although the authors' patients had bilateral optic nerve involvement on magnetic resonance imaging (MRI), could these bilateral optic neuritis

patients simply be a subset of the cadre of patients seen in the ONTT who are at the end of the curve in the extent of their second eye's involvement, such that it is clinically noticeable to them, and they therefore present as bilateral visual loss? These patients have only been followed for 6–18 months—will they have a similar chance of developing multiple sclerosis over the next 10 years as did the MRI negative ONTT cadre? Or is there something unique about these cases, where one might surmise a molecular mimicry induced autoimmune attack against an antigen in the optic nerves but not elsewhere in the central nervous system? Only time will tell—we need to follow these patients for many years, and track what happens to them in terms of subsequent disease to be sure. These rare cases call for a multi-institution registry to truly determine their ultimate outcome.

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