CASE REPORT

SUCCESSFUL TREATMENT OF BILATERAL VISUAL LOSS CAUSED BY IDIOPATHIC OPTIC NEURITIS IN AN HIV-INFECTED PATIENT

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Optic neuritis is not an uncommon diagnosis in HIV-infected patients, but it is rarely idiopathic. We report a case of a young HIV-infected woman who developed optic neuritis as her presenting manifestation of HIV infection. She had initially experienced sudden-onset right-sided painful visual loss; the left eye had become involved within days. Bilateral swollen discs were apparent on fundoscopy. Investigations were performed for meningitis (including bacterial, cryptococcal, tuberculous and syphilitic types), auto-immune diseases, toxoplasma, rubella, cytomegalovirus, viral hepatitis, HTLV-1/2, HIV-1/2 and syphilis. The only positive result was a reactive HIV enzyme-linked immunosorbent assay. The CD4 count was 85 cells/µl. A post-contrast magnetic resonance imaging scan of the brain illustrated enhancement of the optic nerves. Treatment was 3 days of intravenous methylprednisolone 1 g daily, followed by 11 days of oral prednisone 60 mg daily. Highly active antiretroviral therapy was initiated after 2 weeks. Vision improved from day 6 after commencement of steroid therapy, with ongoing recovery at 5 months.

The human immunodeficiency virus (HIV) manifests in various ways in the eye. Several optic nerve disorders have been described, most commonly resulting from opportunistic infections, neoplasms and inflammatory causes.[1] HIV infection as a direct cause of optic neuropathy has been postulated. It is an uncommon presentation and a diagnosis of exclusion, with only a few case reports and case series in the literature. Mwanza *et al.* describe a sub-group of neurologically symptomatic HIV-infected patients from the Democratic Republic of Congo: optic neuropathies occurred in 31%, although only 7% of cases were ascribed solely to HIV.[1] We present a case of idiopathic optic neuritis in an HIV-infected person.

CASE PRESENTATION

A 26-year-old South African woman presented to the ophthalmology clinic of Dr George Mukhari Hospital in Ga-Rankuwa, Gauteng, on 6 January 2009. Her main complaint was a 1-week history of sudden-onset, painful visual loss that had originated in the right eye and had progressed over a few days to include the left eye. She described the pain as being 'deep within the eye' but unrelated to eye movements. On the second day she had attended her local community clinic, where she had been dispensed chloramphenicol eye ointment, which did not improve the condition.

There was no history of trauma. Her medical, surgical, ophthalmological and family histories were otherwise unremarkable, and she was not receiving any other medications.

General examination revealed a well-looking young woman. Her vital signs, including blood pressure, were within normal limits. Visual acuity of the right eye was recorded as counting fingers at 1 metre (<6/60), and testing with a Snellen visual acuity chart showed that of the left eye to be 6/60. A relative afferent pupil defect was present in the right eye. Extra-ocular movements were full and painless. On fundus examination, bilateral swollen optic discs with flame-shaped haemorrhages were apparent (Fig. 1). There were no cotton wool spots and no macular star in either eye. The cornea, anterior chamber, vitreous and retina were normal, as were intra-ocular pressure readings.

Optical coherence tomography objectively documented bilateral swollen optic discs (Fig. 2). Fluorescein angiography showed hyperfluorescence of the optic discs (Fig. 3).

The chest radiograph was normal. Although there were no unusual findings on computed tomography scanning of the brain, a magnetic resonance imaging scan of the brain illustrated enhancement of the optic nerves post-

Fig. 1. Fundus photo of the right eye. There is blurring of optic disc margins associated with disc haemorrhages indicative of optic nerve swelling. Findings in the left eye were similar.

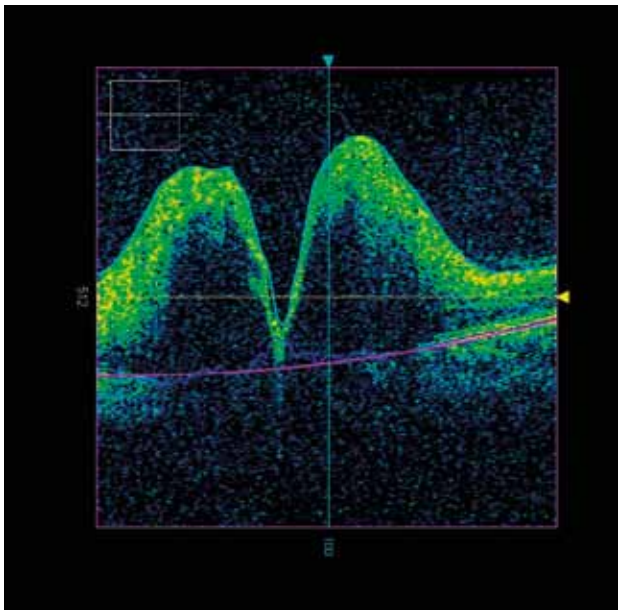

Fig. 2. Optical coherence tomography of the left disc, objectively demonstrating nerve fibre layer swelling at presentation.

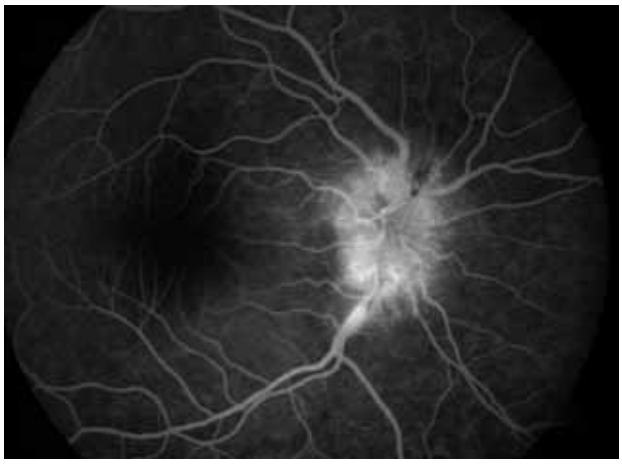

Fig. 3. Fluorescein angiogram of the right eye at presentation. The bright white areas (termed hyperfluorescence) surrounding the optic disc indicate leakage of sodium fluorescein dye and signify disc swelling.

contrast. There were no periventricular plaques and no other abnormalities were noted.

Lumbar puncture was performed and the opening pressure was noted as being within normal range. Cerebrospinal fluid chemistry and cytology were normal. Gram stain and bacterial culture, India ink and latex antigen tests for *Cryptococcus neoformans*, CSF adenosine deaminase (ADA) for tuberculosis and TPHA (*Treponema pallidum* haemagglutinin assay) syphilis tests were all negative.

The full blood count showed slight leukocytosis (white cell count $12\times10^9/1$) and neutrocytosis (83%). The erythrocyte sedimentation rate was slightly increased at 33 mm/h, but the C-reactive protein level was normal at 5.8 mg/l. Auto-immune studies (antinuclear antibodies, antimitochondrial antibodies, antiparietal cell antibodies

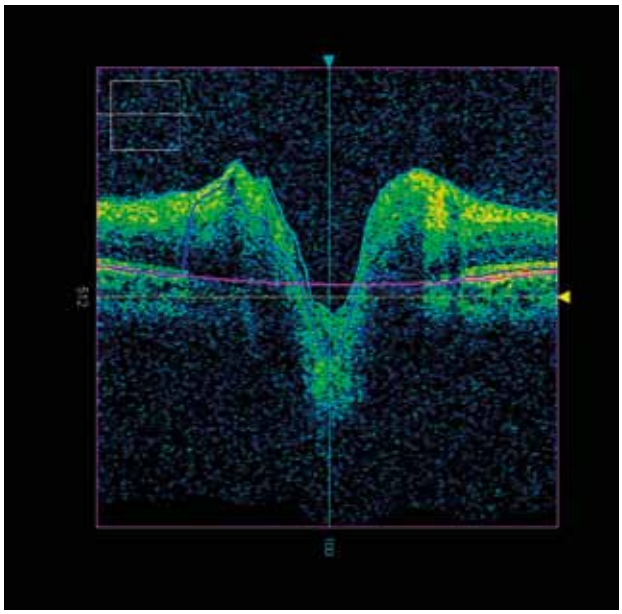

Fig. 4. Optical coherence tomography 2 months after treatment initiation, showing a decrease in disc swelling.

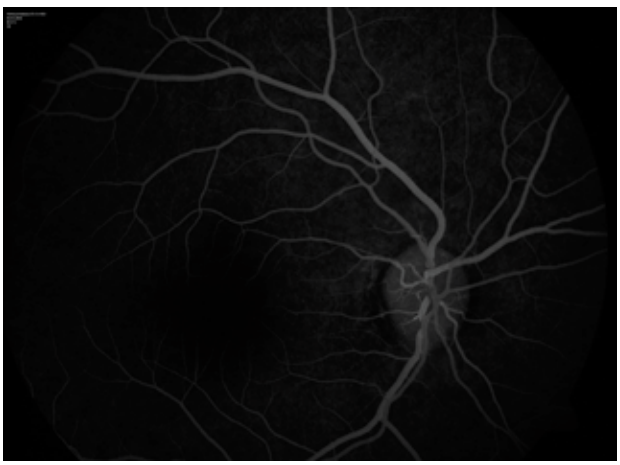

Fig. 5. Fluorescein angiogram of the right eye 2 months after treatment initiation.In comparison with Fig. 3 there is less fluorescein leakage, correlating with resolution of optic disc swelling.

and anti-smooth muscle antibodies) were negative. Serum angiotensin-converting enzyme for sarcoid was also negative. Vitamin B_{12} levels were normal. Tests for mitochondrial mutations associated with Leber's hereditary optic neuropathy were judged unnecessary. Infectious studies were all negative, including blood tests for *Toxoplasma*, rubella, cytomegalovirus (CMV) pp65 antigen, viral hepatitis screen, HTLV-1 and 2, RPR and TPHA for syphilis. The HIV enzyme-linked immunosorbent assay was reactive and the absolute CD4 count was 85 cells/µl.

The patient was admitted on the day of her presentation to our clinic. After 3 days she was treated with intravenous methylprednisolone 1 g daily for 3 days, followed by 11 days of oral prednisone 60 mg daily with subsequent gradual tapering to prevent possible steroid withdrawal symptoms. A diagnosis of idiopathic optic neuritis was subsequently made by exclusion of other causes.

On the 6th day of treatment, the patient reported improvements in her vision. Visual acuity of the right eye was unchanged, but in the left eye it improved to 6/24.

Two and a half weeks after her initial presentation to us, she started highly active antiretroviral therapy (HAART).

At a follow-up visit 2 months after presentation, and 5 weeks after HAART commencement, vision had improved bilaterally to 6/18 on the right and 6/12 on the left. There was complete resolution of disc swelling bilaterally, but some residual optic nerve pallor (Figs 4 and 5).

By the 5th month after presentation, the HIV-1 viral load was suppressed at <25 copies/µl and visual acuity remained 6/18 in the right eye but had improved to 6/6 in the left. The CD4 count improved to 265 cells/µl.

DISCUSSION

Optic neuritis is an inflammation of the optic nerve and a cause of acute visual loss. It may be categorised as typical or atypical.

Typical optic neuritis, the most common type, occurs in demyelinating conditions such as multiple sclerosis (MS). The International Headache Society (IHS) outlines five diagnostic criteria describing dull retrobulbar pain in one or both eyes of maximum 4 weeks' duration accompanied by impaired central or paracentral vision in the absence of a compressive lesion.[4] It has been proposed that the diagnostic criteria be used in conjunction with biomarkers and radiological evidence of multiple sclerosis.[4]

Atypical optic neuritis occurs in non-demyelinating conditions such as viral infections, toxin exposure, meningitis, tumour metastases, syphilis and neuromyelitis optica (Devic's disease), and in some cases it is idiopathic.[3] Features suggesting atypical optic neuritis include age (<12 years or >50 years), African or Asian race, bilateral disease, severe (no light perception) or progressive (>2 weeks) visual loss, unusual description of pain (painless visual loss or severe pain that restricts eye movements or wakes patient from sleep), unusual ocular findings (marked anterior and/or posterior segment inflammation), lack of any visual recovery within 5 weeks or continued deterioration in visual function, symptoms or signs of a systemic disorder other than MS, and corticosteroid-dependent optic neuropathy (deterioration in vision when corticosteroids are withdrawn).[5]

This patient had features suggesting an atypical optic neuritis, particularly haemorrhages that accompanied optic disc swelling. In addition to tests for auto-immune diseases, sarcoidosis, rubella, viral hepatitis and HTLV-1 and 2, investigations for opportunistic infections should also be done in the setting of HIV, and the possibility of false-negative results should be borne in mind. More sensitive tests include serum or CSF cryptococcal antigen for the fungus *C. neoformans*, serology for the protozoan *Toxoplasma gondii*, and pp65 antigen for CMV. Tests which should be interpreted with more caution include syphilis serology, which may revert to negative in HIV infection,[10] and tuberculosis tests because – despite the availability of multiple methods of investigation including microscopy, culture, CSF ADA and imaging – tuberculosis is noted to be cryptic in HIV infection.

Neuro-ophthalmic manifestations of HIV tend to present at an advanced stage of the disease when CD4 cell counts are depleted below 200 cells/µl.[6] Indeed, in patients with AIDS there is a 3 - 8% prevalence of neuro-ophthalmic diseases including eye movement disorders, cranial nerve palsies, neuroretinitis, retrobulbar optic neuropathy, anterior optic neuropathy, papilloedema, visual field defects, cortical blindness, optic atrophy and optic neuritis.[1] The latter manifestation was the presenting illness of HIV in our patient, who reported no prior HIV-related diseases even though her CD4 count at presentation was 85 cells/µl.

In HIV-infected patients, opportunistic infections such as syphilis, toxoplasmosis, tuberculosis and cytomegalovirus are by far the most common cause of optic nerve disorders.[7,8] In rare cases, mostly affecting males, mitochondrial toxicity caused by nucleoside reverse transcriptase inhibitor antiretroviral drugs such as stavudine and didanosine may trigger acute painless central visual loss if the 14484 mitochondrial DNA mutation of Leber's hereditary optic neuropathy is present.[9] We did not test for this mutation because the patient had not been on antiretroviral drugs, was not male, and had no family history of sudden visual loss.

To our knowledge at least 10 cases of idiopathic HIV-associated optic neuritis have been reported in the English literature.[8,10-14] In the 6 instances where CD4 counts were documented, they were well below 350 cells/µl in all cases except one of acute HIV syndrome. Nine of these 10 patients presented with decreased visual acuity in one or both eyes. Of the 9 cases where

visual outcomes were reported, there was improvement in 16 eyes and 2 eyes remained unchanged.

A direct causal link between HIV and optic neuritis has been suggested previously.[10] The mechanism by which HIV could cause primary optic neuritis remains unclear despite much research devoted to neurodegeneration in HIV infection.[1,10,11,15,16] The current widely accepted theory suggests that the pro-inflammatory cytokine tumour necrosis alpha (TNFα) plays a key role.[1,8,11] Other proposed mechanisms include damage secondary to activated microglia and macrophages releasing neurotoxic agents.[1] Consistent with this proposed inflammatory pathogenesis, steroid responsiveness is thought to be a feature of idiopathic optic neuritis in HIV-infected persons.[7,10]

The use of steroids in typical optic neuritis is well established. The prospective randomised and controlled Optic Neuritis Treatment Trial reported that oral prednisone alone had no benefit over placebo and may increase the future risk of repeat episodes of optic neuritis, while intravenous methylprednisolone 1 g daily for 3 days followed by 11 days of oral prednisone 1mg/kg/day was associated with slightly faster visual recovery compared with placebo.[17] Nevertheless, visual recovery within 2 weeks was marked for most participants, regardless of treatment arm.[17]

Treatment for atypical optic neuritis includes treating the underlying cause. The optimal treatment for optic neuritis in HIV- infected patients is controversial. On the one hand, spontaneous resolution of optic neuritis in HIV-infected patients after 2 weeks has been reported[12] and some (but not all) studies have demonstrated accelerated disease progression with the use of even short courses of immunosuppressive doses of steroids in patients with advanced HIV.[18] On the other hand, there are reported cases – ours being one of them – of visual recovery soon after the introduction of systemic steroid therapy.[7,10] It is also possible that antiretroviral therapy contributed to visual recovery in the medium term.[7,8,11]

Some authorities advocate the inclusion of penicillin at neurosyphilis treatment doses as part of empiric management for optic neuropathies of cryptic origin in HIV-infected individuals,[7,10] but we did not employ this strategy. The rationale underlying this approach reflects the attenuating sensitivity of laboratory tests for treponemal infection, which are antibody tests and may be non-reactive in advanced HIV illness.[7]

CONCLUSIONS

Underlying HIV should be considered in cases of atypical optic neuritis in patients at risk. Although uncommon, idiopathic optic neuritis in HIV-infected persons is a diagnosis of exclusion when there is a presentation of sudden visual loss and optic disc swelling. Management must include assessment for HAART, as the condition is linked with advanced disease. It may be reasonable to inform HIV-infected patients with optic neuritis about the possible risks versus benefits of steroid therapy and invite them to consent to the treatment of their choice.

Competing interests. The authors declare that they have no competing interests.

Author contributions. CC acquired and interpreted the data and drafted the manuscript. BM and FL critically revised ophthalmological and HIV-related sections of the manuscript, respectively. AP provided final review and approval of the manuscript.

Ethical considerations. The patient provided voluntary written informed consent to have her anonymous case details published.

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