CASE REPORT

Bilateral optic neuropathy associated with cryptococcal meningitis in an immunocompetent patient

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Accepted 25 May 2014

SUMMARY

Cryptococcal meningitis is associated with significant morbidity and is rare among immunocompetent patients. Clinical presentation as well as the course of disease is usually indolent which may delay the diagnosis. We present the case of a 52-year-old woman admitted with headaches, vomiting and fatigue for 3 weeks. She was diagnosed with cryptococcal meningitis and treated with antifungal therapy. She was referred for ophthalmological examination presenting with decreased vision in the left eye (OS; count fingers), left relative afferent pupillary defect and bilateral sixth nerve palsy. Funduscopy revealed florid bilateral papilloedema. Cranial MRI showed indirect signs of intracranial hypertension as well as multiple parenchymal lesions and optic nerve sheath enhancement after contrast administration. A ventriculoperitoneal shunt was placed. In spite of the control of intracranial pressure there was a decrease in vision in the right eye (OD) and deterioration of visual fields. Intravenous methylprednisolone was used to reverse optic neuropathy and to prevent OD visual loss.

BACKGROUND

Cryptococcosis is caused by *Cryptococcus neoformans*, an encapsulated saprophytic yeast-like fungus.^{1 2} Human infection is usually acquired by inhalation of aerosolised organisms from contaminated particles/soil.² The primary pulmonary infection may be asymptomatic but can be followed by haematogenous spread to other areas of the body.^{1 2} The most common clinical syndrome is meningo-encephalitis.¹⁻³ Ocular involvement occurs in 36–40% of cases of cryptococcosis and is usually secondary to intracranial involvement.^{2 4} It may manifest as papilloedema, optic atrophy and ophthalmoplegia secondary to raised intracranial pressure and/or direct infiltration of the optic nerve.⁴⁻⁶ We present a case of bilateral, asymmetric optic neuropathy secondary to high intracranial pressure and optic nerve infiltration due to cryptococcal meningitis in an immunocompetent patient in which intravenous methylprednisolone was used to reverse optic neuropathy and to prevent contralateral visual loss.

CASE PRESENTATION

A 52-year-old Brazilian woman living in Portugal for 7 years, without any relevant medical history, presented with severe headache, nausea, vomiting, photophobia and fatigue. A cranial CT scan performed at that time was reported as normal and the

patient was medicated with analgesics without improvement.

On admission to a local hospital 3 weeks later she was subfebrile (37.5°), had the previous symptoms and was noted to have lost 15.4 pounds. Respiratory, cardiovascular and abdominal examinations were normal. Viral meningitis was suspected and a lumbar puncture performed. Cerebrospinal fluid (CSF) biochemical examination showed severe hyperproteinorrhachia 1008 mg/dL, low glucose concentration 30 mg/dL and pleocytosis 90 cells/ μ L (predominantly lymphocytes). *C. neoformans* was isolated and the patient was started on amphotericin B at a dose of 300 mg/day and flucytosine 1500 mg four times a day. HIV serology was negative.

During the hospitalisation she reported severe headache and diplopia, and the lumbar puncture showed an opening pressure of 520 mm H₂O, without ventricular enlargement on the cranial CT scans. A lumbar-peritoneal shunt was placed in an attempt to improve her symptoms and control intracranial pressure.

She was referred to our hospital only 50 days after the initial admission when we were asked to observe the patient. She reported decreased vision in her left eye oculus sinister (OS). Uncorrected distance visual acuity (UDVA) was 20/60 and corrected distance visual acuity (CDVA) was 20/30 in the right eye oculus dexter (OD) and was count fingers at 1 m in the OS. A bilateral limitation of abduction and a left relative afferent pupillary defect were present. Using Ishihara plates she was able to identify 6 of 13 correctly with her OD, but only the 'test' plate with her OS. Funduscopy (figure 1) revealed bilateral papilloedema,

Figure 1 Fundus photographs showing bilateral established papilloedema (hyperemia, blurring of the optic disc margins, venous congestion of peripapillary vessels and retinal veins, peripapillary haemorrhages, cotton-wool spots and Patton's folds).

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To cite: Portelinha J, Passarinho MP, Almeida AC, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-203451

peripapillary retinal haemorrhages and cotton-wool spots, which were more severe in the OS. Papilloedema secondary to prolonged raised intracranial pressure and infectious infiltration of the optic nerve sheath were suspected. The lumbar-peritoneal shunt was noted to be blocked and was replaced by a ventriculo-peritoneal shunt. Besides the normalisation of the intracranial pressure, the patient reported of decrease of vision. Octopus 101 (Haag-Streit Inc, Koeniz, Switzerland) automated static perimetry detected progression of the defect (figure 2), showing peripheral depression in the OD, an enlarged blind spot and a nasal step. The patient was started on intravenous methylprednisolone 1 g/day for 3 days. After the third day of treatment OD UDVA and CDVA improved to 20/25 and 20/20, respectively. OS CDVA was count fingers. Left relative afferent pupillary defect remained present and colour vision was 12/13 in the OD and 1/13 in the OS. Perimetry showed a global improvement in the threshold sensitivity in the OD (figure 2). Progressively, the papilloedema resolved bilaterally and evolved to optic atrophy in the OS (figure 3).

INVESTIGATIONS

- Lumbar puncture: CSF biochemical examination showed hyperproteinorrhachia 1008 mg/dL, low glucose concentration 30 mg/dL and pleocytosis 90 cells/ μ L (predominantly lymphocytes). Direct and cultural examination of CSF identified *C. neoformans*.
- Antigen titres in the CSF 1:100.
- Chest X-ray revealed opacity in the inferior lobe of the right lung. Thoracic CT scan confirmed the existence of a solitary 35 mm parenchymal nodule in the inferior lobe of the right lung without adenopathy. Flexible bronchoscopy showed no endobronchial lesions, biopsies and bronchial washings were negative for infection or neoplastic cells. CT-guided percutaneous fine-needle aspirates were inconclusive. Thoracotomy with nodule resection revealed a cryptococcal granuloma.
- Cranial CT scans were negative for ventricular enlargement. MRI of the brain (figure 4), performed on day 50 after initial admission, showed increased leptomeningeal enhancement as well as multiple infiltrative parenchymal lesions without oedema that mildly enhanced after intravenous administration of contrast material. Indirect signs of intracranial hypertension such as mild flattening of the posterior

sciera, intraocular protrusion of the prelaminar optic nerve and increased fluid in the optic nerve sheath were bilaterally present. Contrast-enhanced fat-saturated T1-weighted image revealed optic nerve sheath enlargement and enhancement, suggesting infectious infiltration (figure 4).

- Octopus 101 (Haag-Streit Inc, Koeniz, Switzerland) automated static perimetry performed on day 60 after the initial admission revealed a diffuse depression in sensitivity, enlargement of the blind spot and nasal arcuate defect in the OD. Perimetry was not possible to perform in the OS. On day 67 there was deterioration on visual fields—besides the maintenance of the central sensitivity there was a decrease of the peripheral threshold sensitivity, especially in the nasal field. After intravenous methylprednisolone, visual field showed a global improvement in the threshold sensitivity (figure 2).
- The patient reported exposure to pigeon droppings 40 years prior to illness onset.

TREATMENT

- The patient was treated with amphotericin B at a dose of 300 mg/day for 70 days, flucytosine 1500 mg four times a day for 40 days and at day 40 she started fluconazole, which she will maintain (400 mg/day).
- A lumbar-peritoneal shunt was placed at day 37. At day 60 after initial admission, a ventriculoperitoneal shunt was placed to control intracranial pressure.
- At day 68 intravenous methylprednisolone was started (1 g/day for 3 days).
- Pulmonary lesion of the inferior lobe of the right lung was resected on day 128.

OUTCOME AND FOLLOW-UP

After the third day of treatment with intravenous methylprednisolone, OD UDVA and CDVA improved to 20/25 and 20/20, respectively. OS CDVA was count fingers. Left relative afferent pupillary defect remained present and colour vision was 12/13 in the OD and 1/13 in the OS. Perimetry showed a global improvement in the threshold sensitivity in the OD (figure 2). Progressively, the papilloedema resolved bilaterally and bilateral asymmetric optic atrophy ensued, more severe on the OS (figure 3). The patient has now a follow-up of 6 months.

Figure 2 Octopus 101 (Haag-Streit Inc, Koeniz, Switzerland) automated static perimetry of the right eye on day 60 after the initial admission showing a diffuse depression in sensitivity, enlargement of the blind spot and nasal defect; perimetry on day 67 showing deterioration on visual fields with maintenance of central sensitivity and decrease of the peripheral threshold sensitivity, especially in the nasal field. Perimetry after the intravenous methylprednisolone treatment showing a global improvement in the threshold sensitivity.

Figure 3 Fundus photographs showing progressive resolution of the papilloedema with optic atrophy on the OS.

Cranial MRI performed at day 144 after the admission/at day 129 after the beginning of antifungal therapy revealed regression of the majority of the parenchymal lesions and of the meningeal enhancement, no signs of intracranial hypertension and no optic nerve sheath enhancement (figure 5).

DISCUSSION

C. neoformans can infect not only HIV-positive patients and non-HIV-infected immunocompromised patients but also apparently immunocompetent patients.^{1 3 7} Meningitis was found to be more commonly present in immunocompetent patients (80% vs 57.7%, $p=0.07$).⁷ The predilection for the brain and meninges is probably related to the relative absence of antibody, complement activity or other soluble anticryptococcal factors in the CSF fluid and the presence of substances that enhance local cryptococcal proliferation.⁴ Ocular involvement is usually

secondary to intracranial infection.⁴ Some reports postulate that there are two distinct forms of visual loss: the profound visual loss of rapid onset over a short period of time/early in the course of therapy, which is strongly suggestive of optic neuritis with direct invasion and infection of the optic nerve and optic chiasm by *C. neoformans*; and the slow visual loss characterised by a progressive visual loss which may be due to the effects of persistent intracranial pressure.^{1 4-6} In immunocompetent patients visual loss may occur as well due to intense inflammatory cell response to infection in the meninges surrounding the optic nerve (arachnoiditis), with creation of adhesions causing slow strangulation of the nerve and compromise of the vascular supply, which may lead to subacute to chronic optic neuropathy with atrophy and visual field loss that may be partially reversible.^{8 9}

Central nervous system involvement in this patient was probably secondary to the haematogenous spread after reactivation

Figure 4 MRI of the brain (contrast-enhanced fat-saturated T1-weighted and T2-weighted images) showing indirect signs of intracranial hypertension such as mild flattening of the posterior sclera, intraocular protrusion of the prelaminar optic nerve and increased fluid in the optic nerve sheath. Contrast-enhanced image revealed optic nerve sheath enlargement and enhancement, suggesting infectious infiltration.

Figure 5 MRI of the brain (T2-weighted short-tau inversion recovery (T2 STIR) and contrast-enhanced fat-saturated T1-weighted images) showing the reversal of optic nerve sheath enhancement.

from a prior pulmonary infection, as the parenchymal nodule was found to be a cryptococcal granuloma. Optic neuropathy in this patient is probably multifactorial (1) persistent intracranial hypertension, of which diagnosis and control was delayed because of normal findings on cranial CT scans; (2) arachnoiditis due to involvement of the optic nerve sheath (MRI revealed optic nerve sheath enlargement and enhancement after intravenous contrast material administration) and (3) possibly direct cryptococcal invasion of the left optic nerve, which might be the explanation for the asymmetry found between the OD and OS and why intravenous methylprednisolone was able to reverse the arachnoiditis and stop immune optic nerve dysfunction improving visual acuity and visual fields in the OD, and not in the OS.

Seaton and coworkers reviewed the ophthalmic findings in 82 immunocompetent patients in whom *C. gattii* caused 95% of cases.⁸ Visual loss occurred in 52.6% of survivors and was associated with optic atrophy following optic disc swelling in 60.9%.⁸ The poor outcome of *Cryptococcus* infections in

immunocompetent hosts can be the result of delayed diagnosis, suboptimal initial antifungal therapy as well as immune-mediated optic nerve dysfunction.^{4,8}

Early treatment to reduce the intracranial pressure and specific anticryptococcal treatment may help prevent this catastrophic visual loss.⁴ Also, the use of corticosteroids, as reported by Seaton and coworkers and as in our patient, can reduce visual loss and the development of optic atrophy.⁹

Contributors All authors contributed to this case report. JP, MPP, ACA, JMC contributed towards conception and design. JP and ACA collected the data. JP and JMC drafted the manuscript. JP and MPP analysed the data, prepared the figures and edited the manuscript. JP and JMC revised the manuscript and approved the final version of the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- There is little correlation between CT scan changes and the clinical signs of intracranial hypertension.
- Different mechanisms are involved in optic neuropathy associated with cryptococcal meningitis.
- The status of the immune system plays an important role in the pathogenesis of optic neuropathy associated with cryptococcal meningitis.
- Corticosteroids, such as intravenous methylprednisolone, may be beneficial in preventing visual deterioration and the development of optic atrophy following optic disc swelling because of their anti-inflammatory or immunomodulatory effects.

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