CASE REPORT

The Optic Nerve Compartment Syndrome in *Cryptococcus*-Induced Visual Loss

Anand Moodley¹, Neil Naidoo¹, Deneys Reitz², Naren Chetty³, and William Rae⁴

¹Department of Neurology, ²Department of Radiology, ³Department of Ophthalmology, Greys Hospital, Pietermaritzburg, South Africa, and ⁴Department of Medical Physics, University of the Free State, Bloemfontein, South Africa

ABSTRACT

Visual loss in cryptococcal meningitis has been postulated to be due to papilloedema and/or optic neuritis. A 28-year-old human immunodeficiency virus (HIV)-positive female presented with visual loss, swollen optic discs, and elevated intracranial pressure due to cryptococcal meningitis. Computerised tomographic cisternography and T2-weighted magnetic resonance imaging showed occlusion of the peri-optic subarachnoid space and its reopening after serial lumbar punctures. Presumably lowering of the intracranial pressure resulted in equalisation of pressure across the pressure gradient created by the fungal block. This case supports a third mechanism of visual loss in cryptococcal meningitis, namely, an optic nerve compartment syndrome, that seems more plausible as the principal mechanism.

Keywords: Compartment syndrome, cryptococcal meningitis, optic nerve, optic neuritis, papilloedema

INTRODUCTION

Visual loss in cryptococcal meningitis (CM) occurs in 35% of patients.¹ The landmark study by Rex et al. proposed two mechanisms of visual loss, an early optic neuritis model that occurs within 6 days of disease onset and a late papilloedema model that occurs after 4 weeks.² Since then, there have been many case reports supporting or contesting those claims.^{3–6} The overwhelming evidence is that raised intracranial pressure, which occurs in up to 67% of patients, plays a role.^{1,2} Measures to lower intracranial pressure, such as serial lumbar punctures, ventriculo-peritoneal shunts, lumboperitoneal shunts, and optic nerve sheath fenestrations are all associated with improved visual outcome.^{7–9} However, papilloedema occurs in only 22–25% of patients with raised intracranial pressure.^{1,2} So papilloedema alone cannot be entirely responsible for the visual loss. Although optic neuritis has been documented in histopathological cases, its occurrence too is infrequent. We have suggested the possibility of a compartment syndrome

as being more common and the more likely mechanism responsible for visual loss in the setting of raised intracranial pressure by using diffusion-weighted imaging of the optic nerve.¹ We postulate that the compartment syndrome develops from plugging of the peri-optic CSF space by fungal elements at the optic canal level or within the orbital segment of the nerve. The nerve compression at these sites probably results in axoplasmic stasis and optic nerve dysfunction.

Plugging of the peri-optic space by fungi and polysaccharide remnants is facilitated by the presence of septae, trabeculae and pillars within this space. Killer et al. have demonstrated the presence of these anatomical structures within the peri-optic space that are responsible for the compartmentalization of the peri-optic CSF space from the intracranial subarachnoid space (SAS).¹⁰ They have postulated that these structures may account for idiopathic intracranial hypertension (IIH) without papilloedema or asymmetrical papilloedema. We present a case that supports such a theory in CM, which shares similar

Received 3 February 2013; revised 18 February 2013; accepted 4 March 2013; published online 28 May 2013

Correspondence: A Moodley, Department of Neurology, Greys Hospital, Pietermaritzburg, PO Box 13833, Cascades, 3202, South Africa. E-mail: anand.moodley@kznhealth.gov.za

FIGURE 1 Bilateral severe papilloedema with subretinal haemorrhages (Note: Figure 1 of this article is available in colour online at www.informahealthcare.com/oph).

FIGURE 2 Humphrey's visual fields consistent with raised intracranial pressure. Large blind spots noted bilaterally and nasal field constriction noted on the right.

characteristics to IIH as regards raised intracranial pressure, impaired CSF re-absorption, and the lack of hydrocephalus.

CASE REPORT

A 28-year-old human immunodeficiency virus (HIV)-positive black female on antiretroviral therapy presented with culture confirmed CM. Her symptoms included headaches, blurred vision, neck pain, and fever. Of note was that she had no pain on eye movements and no diplopia. She was awake, alert, and cooperative with minimal neck stiffness. Fundoscopy revealed bilateral swollen optic discs with peripapillary subretinal haemorrhages (Figure 1). Her best corrected visual acuity (BCVA) was 6/18 OD and 6/12 OS, colour vision on Ishihara pseudoisochromatic plates was 15/15 OU and her pupils were 3 mm OU in ambient light and reactive to direct and consensual reflexes. Humphrey's visual fields demonstrated enlarged blind spots OU and nasal constriction OD (Figure 2). The rest of her cranial nerves, motor, sensory, and coordination assessment were normal. Visual evoked potential

(VEP) P100 latencies were normal bilaterally (111 ms OD and 108 ms OS).

Magnetic resonance imaging (MRI) brain was normal and MRI orbits showed no signal change within the optic nerve on high resolution 3D T2 imaging (Figure 3A and B). The peri-optic CSF signal was absent bilaterally on the T2 imaging. There was flattening of the posterior pole of the globe and optic disc elevation bilaterally indicative of raised intracranial pressure. Post-contrast T1 SPIR (fat saturation) imaging showed optic nerve sheath enhancement (Figure 4). Her CD4 count was 181, cerebrospinal fluid (CSF) was acellular with normal biochemistry, CSF pressure was elevated at 37 cm H₂O, and cryptococcal antigen and India ink were positive. She had a macrocytic anaemia of 10.2 g/dL. Her vitamin B₁₂ levels were normal, suggesting that the macrocytosis was due to antiretroviral therapy.

Computerised tomographic (CT) cisternography, performed via lumbar puncture, showed good contrast filling of the basal cisterns but stasis of the contrast-loaded CSF at the distal optic nerve sheath before the optic canal (Figure 5). No contrast filling was noted to proceed beyond this block despite having the patient in a Trendelenburg position.

FIGURE 3 Axial T2 high-resolution 3D images of the orbit. There is loss of peri-optic CSF signal on pre-serial lumbar punctures (A, B), and present on (8 weeks later) post-serial lumbar punctures (C, D). (B) A sleeve of CSF entering the optic canal with no continuation into the orbital segment of the optic nerve (arrow). (D) Reopening of the peri-optic CSF space with narrowing and filling defects noted at the distal part of the orbital segment of the optic nerve (arrow).

FIGURE 4 Pre- (A) and Post- (B) contrast T1 SPIR (fat saturation) images of the orbit showing only optic nerve sheath enhancement.

She was managed with intravenous amphotericin B (0.7 mg/kg/day) for 2 weeks followed by consolidation therapy with oral fluconazole 400 mg daily. Serial lumbar punctures were offered to relieve the intracranial pressure, which was normalized after three lumbar punctures. At 8 weeks follow-up, her headaches had completely cleared and BCVA improved to 6/12 OD and 6/7.5 OS. CSF pressure was noted to be normal before the repeat MRI, which showed unblocking and refilling of the peri-optic CSF space (Figure 3).

DISCUSSION

The patient's clinical presentation is consistent with raised intracranial pressure from CM. Her swollen optic discs, subretinal haemorrhages, and visual field

defects are consistent with raised intracranial pressure, whereas the intact pupillary reflexes, colour vision, VEP, and absence of optic nerve signal change on MRI make optic neuritis very unlikely. MRI brain showed no other cause for raised intracranial pressure apart from CM. The absence of CSF signal surrounding the optic nerve on T2-weighted imaging (Figure 2) and the stasis of contrast filled CSF at the orbital segment of the optic nerve (Figure 5) suggest complete plugging of the peri-optic space by cryptococcal fungal elements. The result would be a large pressure gradient created by this blockage between the significantly elevated intracranial pressure within the intracranial subarachnoid space (SAS) and the pressure of the proximal peri-optic CSF space. A compartment syndrome would thus follow, causing optic nerve compression, axoplasmic stasis, and optic nerve dysfunction that manifests with visual blurring.

FIGURE 5 CT Cisternography. (A, C) No contrast-loaded CSF in the peri-optic CSF space. (B, D) Bilateral stasis of contrast-loaded CSF at the distal part of the optic nerve sheath before the optic canal (arrows).

Killer et al. have shown that the peri-optic SAS is occupied by a network of trabeculae, septae, and pillars comprising fibroblasts and blood vessels.¹¹ They provide histological evidence that the peri-optic SAS narrows in the midorbital segment where the delicate trabeculae changes into broader septae and stout pillars that subdivide the SAS into compartments. The SAS within the intracanalicular segment is extremely narrow and consists of pillars and trabeculae only. The likely sites of occlusion are therefore the midorbital and the intracanalicular segments of the peri-optic SAS.

Killer et al. also suggest that the varying anatomy of these SA trabeculae, septae, and pillars between the two optic nerves account for the asymmetrical papilloedema in IIH.¹² Asymmetrical pressure is transmitted to the lamina cribrosa of the two optic nerves. Therefore, on the side with more trabeculae, septae, and pillars, a lower pressure is transmitted to the optic nerve head and hence little or no papilloedema ensues. We have expanded on this theory in CM, where in addition to raised intracranial pressure there is loading of the peri-optic SAS with fungal elements (the organism and fragments of the polysaccharide capsule). CM is a pauci-inflammatory disorder and fungal loading in the peri-optic CSF space has been shown by histology of the optic nerve sheath during optic nerve sheath fenestration.⁹ The blockage at the midorbital or intracanalicular

segments by the raised pressure and fungal elements creates compartmentalisation between the optic nerve and intracranial SAS. The raised pressure perhaps causes compression of the trabeculae, septae, and pillars against each other, creating a block by a valve-like mechanism. When intracranial pressure is then lowered, there is reopening of the channels between the trabeculae and septae and reestablishment of CSF flow.

Axoplasmic stasis and mitochondrial dysfunction within the axons develop from compression at the site of blockage. We postulate that the development of papilloedema in CM develops from raised intracranial pressure that reaches the lamina cribrosa in some patients but not all, depending on the anatomy of the trabeculae and septae in the peri-optic SAS. No doubt, papilloedema plays a role in visual loss in CM but not exclusively. It is likely that the majority of patients with optic nerve dysfunction in CM, with and without papilloedema, have optic nerve compression at the orbital segment and/or the optic canal level. We further postulate that the extent of axoplasmic stasis determines the presence of papilloedema, which develops when stasis reaches the optic nerve head; a phenomenon that will explain the disparity between the frequencies of elevated intracranial pressure, visual loss and papilloedema in CM.

This case provides good support for the compartment syndrome of the optic nerve in CM and needs

further study. The optic nerve compartment syndrome addresses many deficiencies of the papilloedema and optic neuritis models. Papilloedema is partly responsible for visual loss but nerve compression downstream resulting in large pressure gradients and a compartment syndrome seems to explain the optic nerve dysfunction on diffusion-weighted imaging and the absence of signal changes on T2 imaging.¹ The absence of optic nerve sheath dilatation and surrounding CSF signal is perhaps due to fungal loading in the peri-optic CSF space. Optic neuritis as a cause for visual loss in CM is well documented but rare and possibly develops from a perineuritis. The pauci-inflammatory state of CM in HIV-infected immunosuppressed patients is further support for the infrequent occurrence of optic neuritis in CM.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Note: Figure 1 of this article is available in colour online at www.informahealthcare.com/oph.

REFERENCES

- [1] Moodley A, Rae W, Bhigjee A, Loubser N, Michowicz A. New insights into the pathogenesis of cryptococcal induced visual loss using diffusion-weighted imaging of the optic nerve. *Neuro-ophthalmology* 2012;36:186–192.
- [2] Rex JH, Larsen RA, Dismukes WE, Cloud GA, Bennett JE. Catastrophic visual loss due to *Cryptococcus neoformans* meningitis. *Medicine (Baltimore)* 1993;72:207–224.
- [3] Claus JJ, Portegies P. Reversible blindness in AIDS-related cryptococcal meningitis. *Clin Neurol Neurosurg* 1998;100:51–52.
- [4] Graybill JR, Sobel J, Saag M, van der Horst C, Powderly W, Cloud G, Riser L, Hamill R, Dismukes W. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. *Clin Infect Dis* 2000;30:47–54.
- [5] Kestelyn P, Taelman H. Visual loss and cryptococcal meningitis. *Trans R Soc Trop Med Hyg* 1997;91:727–728.
- [6] Corti M, Solari R, Cangelosi D, Dominguez C, Yampolsky C, Negroni R, Arechavala A, Schtirbu R. Sudden blindness due to bilateral optic neuropathy associated with cryptococcal meningitis in an AIDS patient. *Rev Iberoam Micol* 2010;27:207–209.
- [7] Macsween KF, Bicanic T, Brouwer AE, Marsh H, Macallan DC, Harrison TS. Lumbar drainage for control of raised cerebrospinal fluid pressure in cryptococcal meningitis: case report and review. *J Infect* 2005;51:e221–e224.
- [8] Petrou P, Moscovici S, Leker RR, Itshayek E, Gomori JM, Cohen JE. Ventriculoperitoneal shunt for intracranial hypertension in cryptococcal meningitis without hydrocephalus. *J Clin Neurosci* 2012;19:1175–1176.
- [9] Milman T, Mirani N, Turbin RE. Optic nerve sheath fenestration in cryptococcal meningitis. *Clin Ophthalmol* 2008;2:637–639.
- [10] Killer HE, Jaggi GP, Flammer J, Miller NR, Huber AR, Mironov A. Cerebrospinal fluid dynamics between the intracranial and the subarachnoid space of the optic nerve. Is it always bidirectional? *Brain* 2007;130:514–520.
- [11] Killer HE, Laeng HR, Flammer J, Groscurth P. Architecture of arachnoid trabeculae, pillars, and septa in the subarachnoid space of the human optic nerve: anatomy and clinical considerations. *Br J Ophthalmol* 2003;87:777–781.
- [12] Killer HE, Jaggi GP, Miller NR, Huber AR, Landolt H, Mironov A, Meyer P, Remonda L. Cerebrospinal fluid dynamics between the basal cisterns and the subarachnoid space of the optic nerve in patients with papilloedema. *Br J Ophthalmol* 2011;95:822–827.