Cryptococcal Meningitis Resulting in Irreversible Visual Impairment in AIDS Patients - A Report of Two Cases

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ABSTRACT

Cryptococcus neoformans is the leading cause of meningitis in patients with Acquired Immune Deficiency Syndrome (AIDS) and is associated with high mortality rate. Presenting symptoms include fever, nausea and vomiting, altered mentation, headache and meningismus. Cryptococcal meningitis is not infrequently complicated by raised intracranial pressure and visual sequelae (sometimes by blindness). In patients who survive the infection, the most debilitating outcome appears to be visual impairment or blindness. Management of impending visual complication combines medical and surgical treatment modalities. We report two cases of cryptococcal meningitis associated with visual impairment.

Keywords: cryptococcal meningitis, visual impairment, AIDS

INTRODUCTION

Cryptococcus neoformans is an ubiquitous yeast-like fungus with a polysaccharide capsule, which causes a serious infection with high mortality[1-2] despite standard treatment[1] in patients with AIDS. It is an important AIDS-defining condition, generally occurring in patients whose CD4 cell counts are below 100 cells/UL. In Singapore, 6% of AIDS patients had cryptococcal meningitis and 2.5% presented with this infection as the initial AIDS-defining illness[3].

We report two cases of cryptococcal meningitis in AIDS patients who responded to therapy but unfortunately developed residual complications of visual impairment and blindness, a sequelae not previously reported in local patients. We also discuss the pathogenesis and management of this dreaded complication.

Case Report 1

A 39-year-old Chinese man presented with bitemporal headache, giddiness and vomiting over a period of two days. He had no past medical history of note.

On admission, he was noted to have fever, oral thrush and oral hairy leukoplakia. He was conscious and there was no neck stiffness, papilloedema or any focal neurological signs.

Computed tomographic (CT) scan of the head was essentially normal. Lumbar puncture showed opening and closing pressures of 15 cm and 5 cm respectively, and the cerebrospinal fluid (CSF) was clear. CSF examination revealed the following: White cell count was 4 cells/mm^3 with occasional lymphocytes, total CSF protein 153 mg/dL, no acid fast bacilli were seen and CSF VDRL was negative. There was no cryptococcus detected by Indian ink examination of the CSF but CSF culture subsequently grew *Cryptococcus neoformans*. His serum cryptococcal antigen titre was 1/512.

The patient tested positive for human immunodeficiency virus (HIV) infection with an absolute CD4 count of 16 cells/mm^3. The patient was treated with IV amphotericin B, and then switched to fluconazole. He responded to treatment and was discharged well 18 days post-admission.

About 10 days post-discharge, the patient was noted to have severe bilateral papilloedema during an ophthalmic evaluation (done as a routine for patients with an AIDS-defining illness and a CD4 cell count of below 50 cells/mm^3). At that point in time, he did not have visual symptoms nor early symptoms of raised intracranial pressure (ICP). A CT scan of the head was done which excluded hydrocephalus and radiological signs of raised ICP. We continued non-surgical management with close monitoring of visual fields and medical treatment with oral acetazolamide after consultation with the neurosurgeon.

The patient was subsequently followed up closely by the opthalmologist with repeated visual field assessments. Fundoscopy during a follow-up visit six weeks from the initial eye screen showed blurring of both optic disc margins. Although the patient did not complain of visual symptoms, a detailed visual perimetry assessment showed dramatic and generalised concentric diminution of visual field in both eyes. CT scan of the head then was normal and a decision was made to perform a lumboperitoneal shunt to relieve the effects of raised ICP and to prevent further visual impairment. The patient was well post-operatively and his visual acuity was 6/6. He was discharged on the sixth post-operative day. Except for diminished visual fields, functional status as far as visual ability is concerned was normal at the time of discharge. Future plans include follow-up by the opthalmologist with close monitoring of visual status.

Case Report 2

A 36-year-old Chinese man who had no past medical history of note presented with subacute onset of severe headache over a period of four days and inability to recognise his family members on the day of admission. There was neither fever, photophobia nor other localising symptoms.

On examination, he was noted to be slightly drowsy. Vital signs were stable and oral thrush was noted. He had no focal neurological deficit and pupils were 3 mm, equal in size and reactive to light. There was neither papilloedema nor any neck stiffness. No cranial nerve palsies were noted.

A CT scan of the head done was normal. Lumbar puncture performed showed an opening pressure of 20 cm CSF. CSF microscopy with Indian ink examination showed cryptococcus 3+ and white cell count of 45 cells/UL. Serum cryptococcal antigen was positive with titres > 1/512. CSF culture grew *Cryptococcus neoformans*. The patient was started on IV amphotericin B. The patient subsequently tested positive for HIV with a CD4 cell count of 34 cells/mm^3.

Eight days after starting IV amphotericin B therapy, he complained of bilateral blurring of vision and had a generalised tonic clonic convulsion lasting 15 minutes. His pupils were noted to be mid-dilated and sluggishly reactive to light. Fundoscopy revealed no papiloedema. A repeat CT scan of the head showed no scan evidence of raised intracranial pressure.

A repeat lumbar puncture showed raised opening CSF pressure of more than 40 cm and 20 mLs of CSF was withdrawn. Subsequently, lumbar punctures were performed daily as a therapeutic measure to relieve raised CSF pressure. Opening pressures were persistently greater than 40 cm CSF and each time, about 15 mLs to 20 mLs of clear CSF was withdrawn.

The patient's eyesight continued to deteriorate over the next few days until neither eye had light perception. Magnetic resonance imaging (MRI) of the optic pathway revealed no abnormality.

A lumboperitoneal shunt was inserted to alleviate raised intracranial pressure. The patient remained stable and received a course of IV amphotericin B in combination with flucytosine.

Unfortunately, he developed irreversible blindness in both eyes, the most probable cause of which was thought to be compressive optic neuropathy secondary to raised intracranial pressure.

DISCUSSION

The implicated organism in cryptococcal meningitis is an encapsulated yeast-like fungus with two varieties, *var neoformans* and *var gattii. C neoformans var gattii* is associated with a higher incidence of visual impairment, as compared to *C neoformans var neoformans.* However in Singapore, laboratory speciation of *C neoformans* into *var gattii* and *var neoformans* is not routinely performed.

Cryptococcal meningitis may result in elevated CSF pressure as seen in these two patients, who present with decreased visual acuity, papilloedema and an enlarged blind spot. Lumbar puncture often reveals high opening CSF pressure, even in the absence of radiological hydrocephalus.

Visual loss and some of the cases of death early after the onset of chemotherapy may be related to high CSF pressure, regardless of antifungal therapy[4]. Raised ICP should be managed actively to prevent visual impairment[5]. Signs of raised ICP include deteriorating consciousness, headache, vomiting or visual disturbances. Late signs include mental obtundation and false localising cranial nerve signs.

Acetazolamide has been advocated to inhibit CSF production especially in AIDS patients in whom ventriculo-peritoneal shunting carries additional risks[5]. One study[6] involving immunocompetent individuals demonstrated that corticosteroids did appear to be of value in preventing or halting visual loss.

If hydrocephalus is present, ventricular shunting may then prove beneficial. Frequent high volume (25 mLs to 30 mLs of CSF) lumbar punctures have been successfully performed in a small number of such patients[4,5]. The two patients discussed had lumboperitoneal drains inserted to divert CSF but this, unfortunately, did not reverse the development of visual impairment. The timing of surgery may be crucial in the management of such cases. One study[7] suggested that the duration of disturbance of consciousness or change of mentality before shunting is critical in the determination of the outcome of surgery. It is suggested that low CSF protein concentration was a favourable indicator for surgery, that active stage of cryptococcal meningitis does not contraindicate the necessity of shunting and premedication with antifungal drugs is unnecessary.

One study[8] noted that in survivors of cryptococcal meningitis, the only morbidity was that of visual impairment or blindness and this was attributed mainly to intracranial hypertension with residual deficits determined by the measures taken to lower intracranial pressures.

Visual loss in patients with cryptococcal meningitis could be attributed to either direct spread of inflammation to the optic nerves (optic neuritis), or compressive optic neuropathy secondary to raised ICP[9]. Optic neuritis is characterised by the onset of profound visual loss over a period as short as 12 hours before or early in the course of therapy. In cases of such rapid visual loss, direct invasion of the optic nerve by *C neoformans* was demonstrated[9]. There may be no obvious endophthalmitis or cryptococcomas in the visual pathway[9] but microscopic invasion of the optic nerves and tracts may occur bilaterally.

Raised intracranial pressure, on the other hand, typically causes slow but progressive visual loss, which typically begins later during therapy. While the initial deficit may be mild, patients with slow visual loss can progress to severe visual loss over weeks to months. The only factors that appear to predict either pattern of visual loss are the presence of papilloedema, an elevated CSF opening pressure, and a positive CSF India ink preparation. The only therapeutic measures with any degree of consistent success were those directed at reducing intracranial pressure. When begun early and used aggressively, such therapy halted and sometimes even reversed the course of visual loss, particularly in the slow visual loss group.

One study[10] showed that cerebrospinal fluid shunting was much more successful than serial lumbar punctures or the use of high-dose dexamethasone and that patients with acquired immunodeficiency syndrome who develop cryptococcal meningitis and who suffer serious visual loss or ocular palsies with elevated pressures should be considered for cerebrospinal fluid shunting at an early stage.

In our local cohort of AIDS patients, the average survival period in patients with cryptococcal meningitis is 313 days[3]. Since visual impairment/ blindness may affect the quality of life in patients who recover from an acute infection, careful attention must be paid to the management of raised intracranial pressure and the prevention of visual complications.

CONCLUSIONS

Visual impairment or blindness is a well documented complication following cryptococcal meningitis. The two factors which predict the development of this dreaded complication appear to be raised intracranial pressure and direct invasion of the optic pathway/optochiasmatic arachnoiditis. The species of *C neoformans var gattii* particularly appears to be a determinant in immunocompetent patients. Aggressive and timely medical treatment of the primary CNS cryptococcosis as well as neurosurgical management of raised ICP with diversional shunting may improve visual outcomes in such patients.

REFERENCES

1. Seaton RA. The management of cryptococcal meningitis in Papua New Guinea. P N G Med J 1996; 39:67-73.
2. Sugar A, Stern JJ, Dupont B. Overview: treatment of cryptococcal meningitis. Rev Infect Dis 1990; 12 Suppl 3:S338-S348.
3. Clinical Epidemiology, National HIV Registry, Tan Tock Seng Hospital, Singapore.
4. Denning DW, Armstrong RW, Lewis BH, Stevens DA. Elevated cerebrospinal fluid pressures in patients with cryptococcal meningitis and acquired immunodeficiency syndrome. Am J Med 1991; 91:267-72.
5. Johnston SR, Corbett EL, Foster O, Ash S, Cohen J. Raised intracranial pressure and visual complications in AIDS patients with cryptococcal meningitis. J Infect 1992; 24:185-9.
6. Seaton RA, Verma N, Naraqi S, Wembri JP, Warrell DA. The effect of corticosteroids on visual loss in Cryptococcus neoformans var gattii meningitis. Trans R Soc Trop Med Hyg 1997; 91:50-2.
7. Bach MC, Tally PW, Godofsky EW. Use of cerebrospinal fluid shunts in patients having acquired immunodeficiency syndrome with cryptococcal meningitis and uncontrollable intracranial hypertension. Neurosurgery 1997; 41:1280-2.
8. Doi SA, Tan CT, Liam CK, Naganathan K. Cryptococcosis at the University Hospital, Kuala Lumpur. Trop Doct 1998; 28:34-9.
9. Rex JH, Larsen RA, Dismukes WE, Cloud GA, Bennett J. Catastrophic visual loss due to cryptococcus neoformans meningitis. Medicine (Baltimore) 1993; 72:207-24.
10. Lalloo D, Fisher D, Naraqi S, Laurenson I, Temu P, Sinha A, Saweri A, Mavo B. Cryptococcal meningitis (*C neoformans var gattii*) leading to blindness in previously healthy Melanesian adults in Papua New Guinea. Q J Med 1994; 87:343-9.