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Medical management of acute loss of vision in tuberculous meningitis: A case report

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ABSTRACT

Blindness and vision impairment are unpredictable complications of tuberculous meningitis (TBM) that are often unrecognized in the acute stages of illness due to inability to assess vision in patients with depressed levels of consciousness or confusion. We present a patient with definite TBM confirmed by positive Xpert MTB/RIF assay of cerebrospinal fluid (CSF) who developed binocular blindness two weeks after diagnosis and initiation of standard anti-tuberculosis treatment (ATT). Ophthalmological exam demonstrated complete bilateral abducens nerve palsies, impaired pupillary responses to light, normal optic discs, and visual acuity of hand motion only in each eye. Brain CT showed progressive enlargement of the third and lateral ventricles. We managed the patient medically with dexamethasone, acetazolamide, and substitution of moxifloxacin for ethambutol. Serial brain CTs confirmed gradual resolution of hydrocephalus. The patient had complete neurological recovery at six months except for residual blindness in the right eye. Visual acuity in the left eye recovered to normal (20/20). The assessment and management of vision impairment in TBM is discussed.

1. Introduction

Tuberculosis (TB) causes a significant burden of disease throughout the world with 10 million estimated incident cases and 1.5 million estimated deaths in 2018 [1]. Tuberculous meningitis (TBM) is the most severe form of TB and carries a high risk of death and serious disability [2,3]. Patients surviving from TBM are often left with chronic neurological impairment as a result of complications including hydrocephalus, strokes, and seizures [4–7]. Vision impairment is a particularly deleterious sequela of TBM that can occur as a consequence of the disease process and/or anti-tuberculosis treatment (ATT) [8]. Here we report a case of TBM complicated by the rapid onset of binocular blindness (World Health Organization (WHO) definition; presenting visual acuity $<3/60$ or 20/400 [9]) that was managed medically with a favorable outcome.

2. Case report

A 25-year-old woman presented to Muhimbili National Hospital, the national referral hospital of Tanzania, with severe headaches, neck pain, fever, confusion and vomiting for one week. On physical exam, she was confused and febrile (39.6 °C) with bilateral cervical adenopathy. Neurological exam demonstrated signs of meningeal irritation and bilateral abducens nerve paralysis. Pupils were symmetrical and normally reactive. Visual acuity and fields could not be assessed due to the patient's restlessness and confusion. Good strength was present in all limbs. Lumbar puncture showed clear CSF with an opening pressure of 30 cm of H_2O. CSF analysis revealed 65 white blood cells/μL (100% lymphocytes), glucose 0.8 mmol/L, and protein 1.97 g/L. CSF Xpert MTB/RIF was positive (very low) with no rifampicin resistance detected. CSF cryptococcal antigen, India Ink preparation, and bacterial cultures were negative. HIV 1/2 serum antibody was negative. Non-contrast CT of the brain showed mild symmetrical ventricular enlargement (Fig. 1A).

The patient was started on standard daily fixed-dose combination tablets of ATT (isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 1600 mg, and ethambutol 1100 mg) with pyridoxine 25 mg once daily. She received intravenous dexamethasone 8 mg three times daily for one week followed by oral dexamethasone starting at 4 mg three times daily. The general condition of the patient improved and she was discharged home with her husband after one week. During a follow-up visit one week later, the patient reported loss of vision in both eyes and

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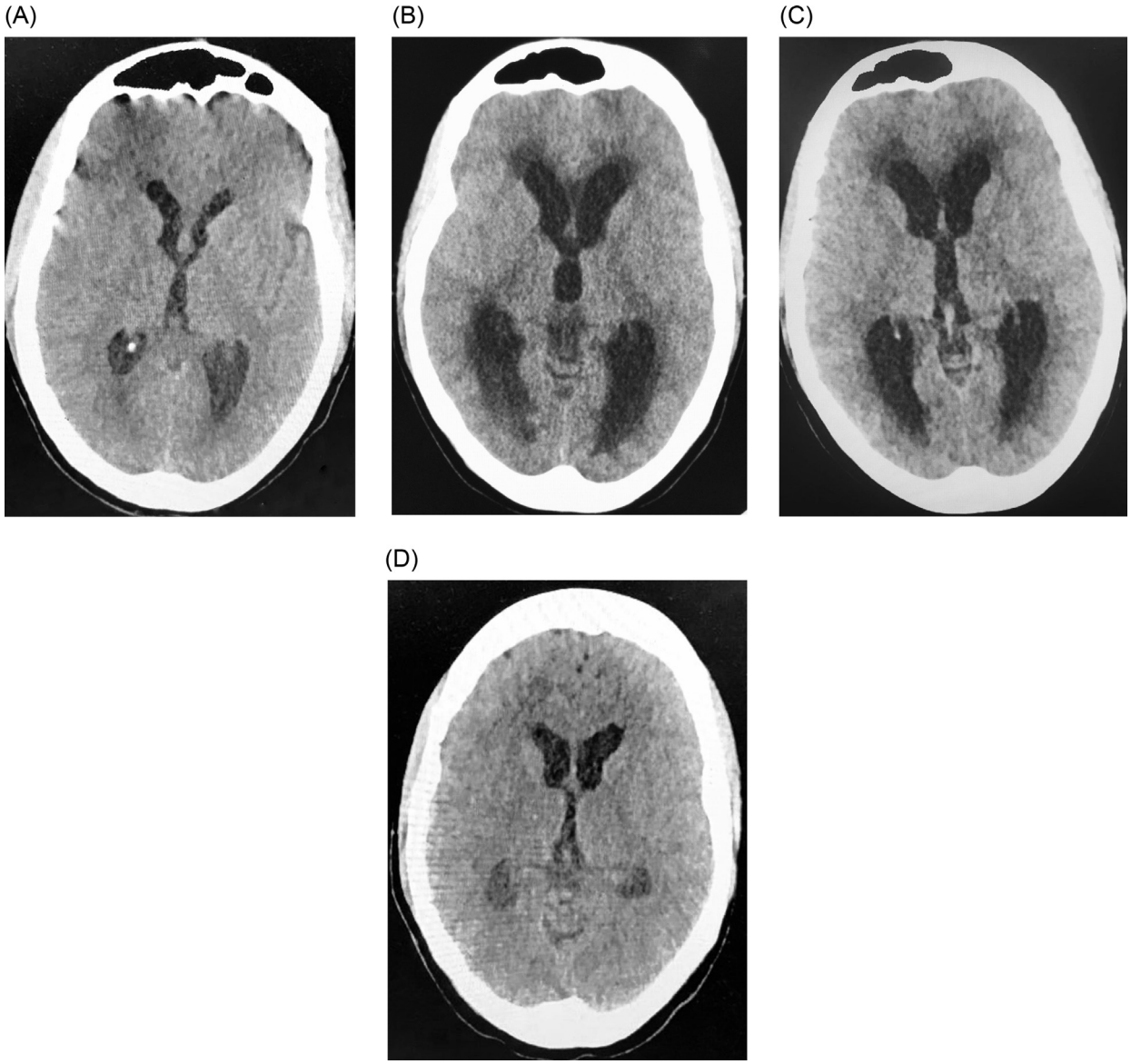

Fig. 1. Non-contrast CT of the brain. (A) admission to hospital; (B) week 2 of ATT; (C) week 6 of ATT; (D) week 11 of ATT. (ATT = anti-tuberculosis treatment).

mild headaches. Her husband confirmed that she had excellent vision in both eyes without the need for corrective lenses prior to the onset of her meningitis. On physical exam, she was alert, oriented, and had normal language function. Ophthalmological exam revealed persistent bilateral abducens nerve palsies (Fig. 2A and B), 5 mm pupils in ambient room lighting with minimal reaction to bright light, normal optic discs on direct funduscopic exam, and visual acuity of hand motion only in the left eye and in the right eye. Gait was wide-based and moderately ataxic. Immediate non-contrast CT of the brain was done and showed a marked increase in hydrocephalus (Fig. 1B).

Ethambutol was stopped and changed to moxifloxacin 400 mg once daily. Isoniazid, rifampicin, and pyrazinamide were maintained at the same doses. Dexamethasone was continued at 4 mg three times daily and acetazolamide was started at 1000 mg twice daily. Non-contrast CT of the brain was obtained after one month and showed improved hydrocephalus (Fig. 1C). Dexamethasone was reduced to 2 mg three times daily and acetazolamide was continued at 1000 mg twice daily. ATT was changed two weeks later to WHO-recommended continuation phase consisting of isoniazid 300 mg and rifampicin 600 mg daily. Complete ophthalmological evaluation was performed the following month and demonstrated visual acuity of 6/5 (20/16) in the left eye and counting fingers only at two meters in the right eye with no improvement using pinhole testing. Color vision was normal in the left eye by the Ishihara test. Funduscopic exam showed mild optic disc pallor on the left and moderate optic disc pallor on the right. Anterior chambers, intraocular pressures, and retinal vessels were normal in both eyes. Visual field testing demonstrated constriction in the left eye (Fig. 3A and B). Retinal nerve fiber layer thickness (RNFL) measured with optical coherence tomography (SOCT Copernicus HR, Zawiercie, Poland) revealed moderate thinning of the right eye (temporal-superior-nasal-inferior thickness (TSNIT) mean = 79 ± 30 μm (S.D.)) and mild thinning of the left eye (TSNIT mean = 87 ± 29 μm). Repeat non-contrast CT of the brain showed continued reduction of the ventricular enlargement (Fig. 1D). Dexamethasone was reduced to 1 mg twice daily.

The patient was seen in follow-up at six months of ATT with resolution of all neurological symptoms except for persistent visual loss in the right eye. Extraocular movements and gait were normal. Visual acuity was 20/20 in the left eye and finger counting at one meter in the right eye. Dexamethasone was reduced to 0.5 mg twice daily and discontinued in two weeks. Acetazolamide was reduced to 500 mg twice daily. The patient will complete six additional months of ATT.

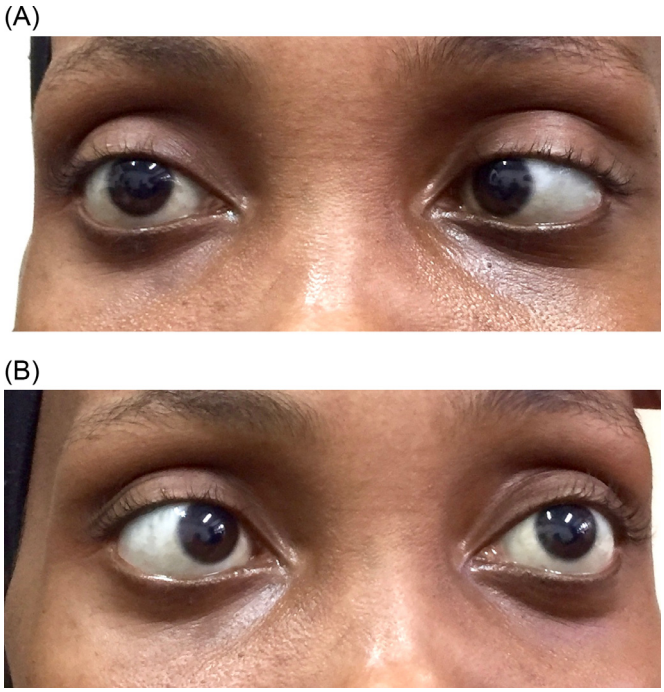

Fig. 2. Bilateral abducens nerve palsies. (A) voluntary gaze to the right; (B) voluntary gaze to the left.

3. Discussion

Vision impairment is a complication of TBM that can occur as a result of multiple processes including compression of the optic chiasm due to hydrocephalus, inflammation and ischemia of the optic chiasm and/or optic nerves due to arachnoiditis, papilledema from increased intracranial pressure, occipital infarction due to vasculitis, and toxic effects of anti-tuberculosis medications [8]. In a prospective study of 101 patients with TBM in India, low vision (visual acuity $<6/18$ but $\geq 3/60$ in the better eye) and blindness (visual acuity $<3/60$ in the better eye) were present at baseline in 19.8% and 4% of patients and in 10.4% and 3.1% of patients after 6 months of ATT [10]. A retrospective cohort study using administrative claims data of 806 patients treated for TBM in the United States reported vision impairment in 17.5% of patients at 6 months [5]. A clinical trial conducted in Vietnam comparing a standard, 9-month ATT regimen with an intensified ATT regimen (higher dose rifampin and levofloxacin for the first 8 weeks) reported a higher frequency of vision impairment (not defined) in the intensified-treatment group (3.4% versus 1.0%) [7].

Hydrocephalus is one of the earliest and most frequent complications of TBM and is often more severe in children [11–15]. Treatment of hydrocephalus is not standardized and different approaches have been advocated. For patients with presumed communicating hydrocephalus, medical treatment combining furosemide, acetazolamide, and corticosteroids with repeated lumbar puncture pressure measurements has been suggested [15–17]. Options for relieving non-communicating (obstructive) hydrocephalus or failed medically-managed communicating hydrocephalus are primarily surgical by insertion of a ventriculo-peritoneal shunt (VPS) or by performing an endoscopic third ventriculostomy [15–18]. Indications for VPS in published studies have been variable [17]; in general, patients with severe obstructive hydrocephalus or hydrocephalus associated with declining clinical status and worsening radiological findings are candidates.

Optochiasmatic arachnoiditis (OCA) and optochiasmal tuberculoma are severe complications of TBM associated with profound visual impairment or blindness [19–21]. In OCA, visual loss results from ischemia of the optic chiasm and/or optic nerves due to basal inflammatory exudates and vasculitis of the vasa nervosum. Optochiasmatic tuberculomas have been reported to develop paradoxically after commencing ATT [22–24]. Vision impairment due to OCA is typically insidious and slowly progressive but has been reported to occur suddenly and rapidly [21]. MRI findings include enhancement involving the optic chiasm, cisternal segment of optic nerves, interpeduncular fossa, pontine cistern, and suprasellar region with or without discrete tuberculomas [25]. Treatment of OCA commonly includes ATT and adjunctive intravenous or oral corticosteroids with complete recovery of vision reported in some cases [21]. Additional therapies such as thalidomide and intrathecal hyaluronidase have been utilized with variable success [21,26]. A select group of patients may benefit from neurosurgical decompression of the optic chiasm although the evidence is limited [21].

Ethambutol hydrochloride is one of the first-line drugs used in the treatment of TB [27]. It is the least toxic of the first-line agents with a reported incidence of drug-related visual impairment of 22.5 per 1000 persons [28]. Ocular toxicity from ethambutol presents as a retrobulbar optic neuritis involving the axial and/or periaxial fibers [29]. Proposed

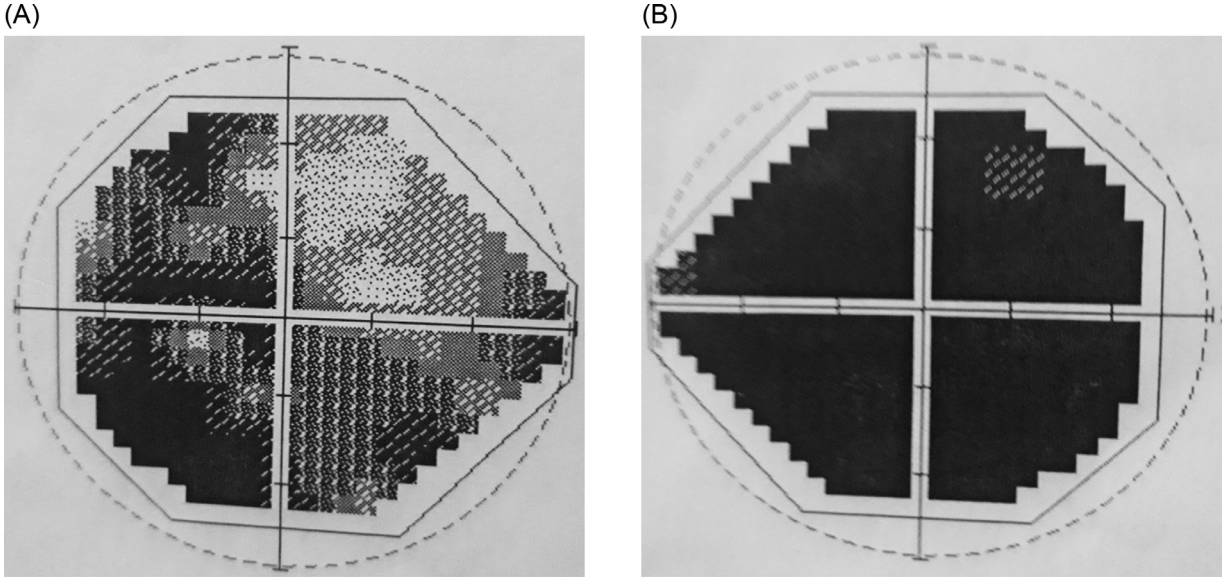

Fig. 3. Automated visual field test (Optopol PTS 1000, Optopol Technology S.A., Zawiercie, Poland). (A) left eye; (B) right eye.

mechanisms include the metal chelating effects of ethambutol and associated disruption of mitochondrial function and excitotoxic pathways involving glutamate [31,32]. Clinical presentation of ethambutol-related optic neuropathy involves bilateral, progressive, painless blurring of vision and decreased color perception [29–31]. Central vision is commonly affected although other visual field abnormalities like bitemporal defects or peripheral field constriction have been reported [33–35]. Optical coherence tomography (OCT) is a technology for measuring the retinal nerve fiber layer thickness that can detect early damage not visible by direct funduscopic examination [36].

Ethambutol ocular toxicity usually develops after several months of exposure but there are reports of severe visual impairment occurring as early as a few days after commencing treatment [37,38]. The incidence of ocular toxicity secondary to ethambutol appears to be dose-related [28,29] and predictors include poor renal function, which leads to failure to excrete the drug hence its accumulation, aging, prolonged duration of ethambutol use, a higher dose, hypertension, diabetes and concurrent optic neuritis related to tobacco and alcohol consumption [31]. Ethambutol should be stopped immediately when significant vision impairment is detected and other anti-tuberculosis agents should be considered [27,29,39,40]. Toxicity can be reversible with most patients recovering vision months after stopping the medication [28,34]. If vision fails to improve after discontinuing ethambutol, isoniazid should also be stopped [40]. Isoniazid is an anti-tuberculosis drug that rarely causes visual impairment due to optic neuropathy [41].

Our patient developed binocular blindness two weeks after diagnosis of and initiation of treatment for TBM. Although brain CT showed an increase in hydrocephalus, we could not conclude that hydrocephalus was the cause for the severe loss of vision. Optochiasmatic arachnoiditis and ethambutol-related optic neuropathy could have caused or contributed to our patient's vision impairment. She was alert, cognitively intact, and ambulatory at the time of the second CT. She did not have papilledema. Therefore, we decided that the risks of surgical treatment of hydrocephalus with ventriculo-peritoneal shunting outweighed the potential benefits and decided to treat her hydrocephalus medically by adding high-dose acetazolamide and maintaining the same dose of dexamethasone with an extended tapering course over six months. In addition, we removed ethambutol and substituted moxifloxacin for the two-month intensive phase. Her outcome was favorable with complete vision recovery in the left eye, residual vision impairment in the right eye, and reduced hydrocephalus.

4. Conclusions

Early assessment and regular monitoring of vision in patients with TBM is recommended. If feasible, a thorough baseline ophthalmologic evaluation should be performed before commencing treatment with ATT that includes ethambutol and/or isoniazid [29,39,40]. Significant visual loss in either eye should prompt repeat brain imaging and ophthalmological consultation. Interventions should include optimization of medical treatment for hydrocephalus and meningeal inflammation in addition to immediate withdrawal of ethambutol. Neurosurgical consultation should be obtained for cases with severe hydrocephalus and for cases with new or enlarging tuberculomas affecting the optic chiasm.

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. Our sincere gratitude goes to the patient and her family for allowing us to share her case.

Declarations of Competing Interest

None.

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