Reversible deafness and blindness in a patient with cryptococcal meningitis in Tanzania

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Abstract

Cryptococcal meningitis is a common and devastating complication of advanced HIV, and is most prevalent in low resource settings in sub Saharan Africa. Raised intracranial pressure is one of the hallmarks of the disease, which can lead to visual and hearing loss and ultimately death. We present the case of a patient with visual and hearing impairment secondary to Cryptococcal meningitis successfully managed by serial cerebrospinal fluid drainage. This case highlights some of the challenges of managing this severe opportunistic infection in a low resource setting.

Introduction

Cryptococcal meningitis (CM) is a common and severe opportunistic infection of advanced human immunodeficiency virus (HIV) infection. It is estimated to cause up to 600,000 deaths per year,[1] primarily in sub Saharan Africa, and is closely linked to the HIV pandemic. CM is always fatal if left untreated, and even with access to antifungal therapy, mortality is up to 40% within 10 weeks.[2] In the age of widespread access to antiretroviral therapy for HIV, surviving CM and subsequently treating the underlying HIV infection can lead to good long-term outcomes. However, treatment of this opportunistic neurological infection is challenging. Prompt antifungal therapy is central to successful treatment however management of raised intracranial pressure is an essential adjunct to therapy. Morbidity and mortality in CM is often related to severely elevated intracranial pressure, which can lead to visual loss, hearing loss and ultimately death.[3] Moreover, the recommended antifungal treatments are often not available in parts of the world most affected by CM,[4] and management of this complex infection presents particular challenges in resource limited settings.[5] Here we describe a patient with severe, advanced CM in a resource-limited setting, which was effectively treated by serial lumbar punctures and intracranial pressure (ICP) control.

Case Report

A 19-year-old female was referred from a remote rural district to a tertiary referral hospital in Tanzania. She had a 3-month history of severe headache, unrelieved by analgesia with deterioration in vision over the previous 6 weeks and progressive bilateral hearing loss. The headache was associated with regular bouts of vomiting. She was known to be HIV positive and had been on antiretroviral therapy for 7 years (Tenofovir, Lamivudine, Efavirenz).

On admission she had a Glasgow Coma Score (GCS) of 15, was afebrile and normotensive. She had no neck stiffness. She was however profoundly blind with no light or dark perception in either eye. She had a marked left sided ptosis with the pupil *down and out*, suggestive of a 3rd cranial nerve palsy. Fundoscopy revealed marked papilloedema bilaterally. She had severe bilateral hearing impairment, able only to hear loud voices at very close proximity. She had normal power, tone and reflexes in all limbs. CD4 count was 100 cells/mm^3. Serum creatinine (62 µmol/L) and ALT (8 U/L) were within normal limits.

Brain imaging not available (the site possessed a CT scanner however it was not functioning at the time due to technical issues) therefore a lumbar puncture was performed despite the papilloedema. Opening pressure (OP) was high at 37cm H_20. The CSF was clear in appearance. The patient reported almost instantaneous relief of headache following the lumbar puncture. CSF analysis was positive for Cryptococcal antigen (lateral flow assay) and encapsulated yeast were seen on Indian Ink staining (Figure 1A). Gram stain was negative. CSF culture was positive for Cryptococcus neoformans on YPD agar (Figure 1B). The patient was initiated on fluconazole monotherapy at a dose of 1200 mg per day due to the unavailability of Amphotericin B. Therapeutic lumbar punctures were performed on days 1, 4, 7 , 14, 18 and 22 , with corresponding opening pressures of 37, 37, 27, 31, 27 and finally 20 cm H_20. On each occasion CSF was drained to a closing pressure of <20 cm. Approximately 10 mL of CSF was removed at each LP. On day 22 the OP was normal at 20 cm H_20. On discharge her ptosis had resolved, her vision was improving to the point where she could discern light and dark and shapes. Her hearing had recovered to almost normal. She received 1200 mg daily of oral fluconazole for the first two weeks, which was then reduced to 400 mg once daily to be continued for 8 weeks, with follow up planned at her local HIV treatment clinic.

Discussion

This case highlights the severe complications of CM, and also several important issues in the management of CM in the developing world, where the vast majority of CM cases are found. The treatment of choice is a combination of Amphotericin B and flucytosine,[6] neither of which are readily available in low resource settings, resulting in the use of suboptimal therapies such as fluconazole monotherapy as in the presented case.[4] Additionally toxicity management is a challenge. Even where Amphotericin B can be obtained, facilities for monitoring electrolytes and renal function are often not available making safe administration problematic.[7] In the presented case, electrolyte measurement was available but regular monitoring was not feasible due to financial constraints.

Raised intracranial pressure is thought to result from decreased reabsorption of CSF mechanically by the *Cryptococcal* organism,

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specifically the capsule of the organism blocks the arachnoid villi.[8] Raised ICP is a major cause of morbidity and mortality in CM and can cause a spectrum of symptoms from severe headaches (the commonest presenting symptom in CM), vomiting, to cranial nerve palsies and blindness and hearing loss as with our patient. Aggressive management of raised ICP by CSF drainage is a vital component in the management of CM, and can be accurately measured by the use of a manometer. The use of manometers are recommended in international treatment guidelines,[6,9] however are usually not available in resource poor setting.[10] Manometers were available in this case, however in the absence of manometers the use of IV tubing as a substitute to measure ICP has been successfully used in a similar low resource setting.[11]

Sixth cranial nerve palsy is the commonest focal neurological deficit encountered in CM, in which it is often a *false localizing* sign secondary to raised ICP, however multiple cranial nerves can be affected and 3rd nerve paresis has been reported in the setting of severely raised ICP.[12] Visual loss in CM can present as acute, catastrophic visual loss, thought to be secondary to optic nerve infiltration by the *Cryptococcus* organism, or a sub-acute process secondary to raised intracranial pressure.[13] Visual loss can be irreversible in up to 50% of cases.[14]

Hearing loss can be caused by either infiltration,[15] or compression of the vestibulocochlear nerve. In this case blindness and deafness were at least partially reversed with repeated CSF drainage in combination with antifungal therapy, albeit suboptimal therapy given the inaccessibility of antifungals other than fluconazole. Reversibility of both the hearing and visual loss is highly suggestive that they were caused at least in part by the severe elevation in ICP.

The lack of access to brain imaging is also a major problem in resource-limited settings. CT imaging of the brain is recommended when and where available, particularly to exclude intracranial mass lesions. However, if the clinical index of suspicion for CM is high in a low resource setting without access to imaging, the balance of risk often favors performing a lumbar puncture. Raised intracranial pressure in this context is not a specific contraindication to LP, and this is reflected in international CM management guidelines.[9] The risk of *coning* or herniation is reduced in CM as the raised ICP generally leads to a communicating rather than non-communicating hydrocephalus (which usually results from CSF flow obstruction), and multiple, high volume drainage of CSF in the specific setting of CM is considered not only safe but an essential component of management.[16]

Conclusions

This case demonstrates that even in severe and advanced cases of CM, aggressive management of raised ICP can significantly improve outcomes and reduce morbidity and mortality. This can be performed by the relatively straightforward and *low-tech* procedure of the lumbar puncture. There is a strong body of evidence that therapeutic LPs improve outcomes in CM, and there is growing evidence that therapeutic lumbar punctures are beneficial in the management of Cryptococcal meningitis even in the absence of raised intracranial pressure and can help to remove cryptococcal antigen.[17,18]

The case also highlights the particular challenges of treating CM in resource-limited settings, which is where the vast majority of cases worldwide are encountered. Successful treatment of CM relies on access to effective, rapid-

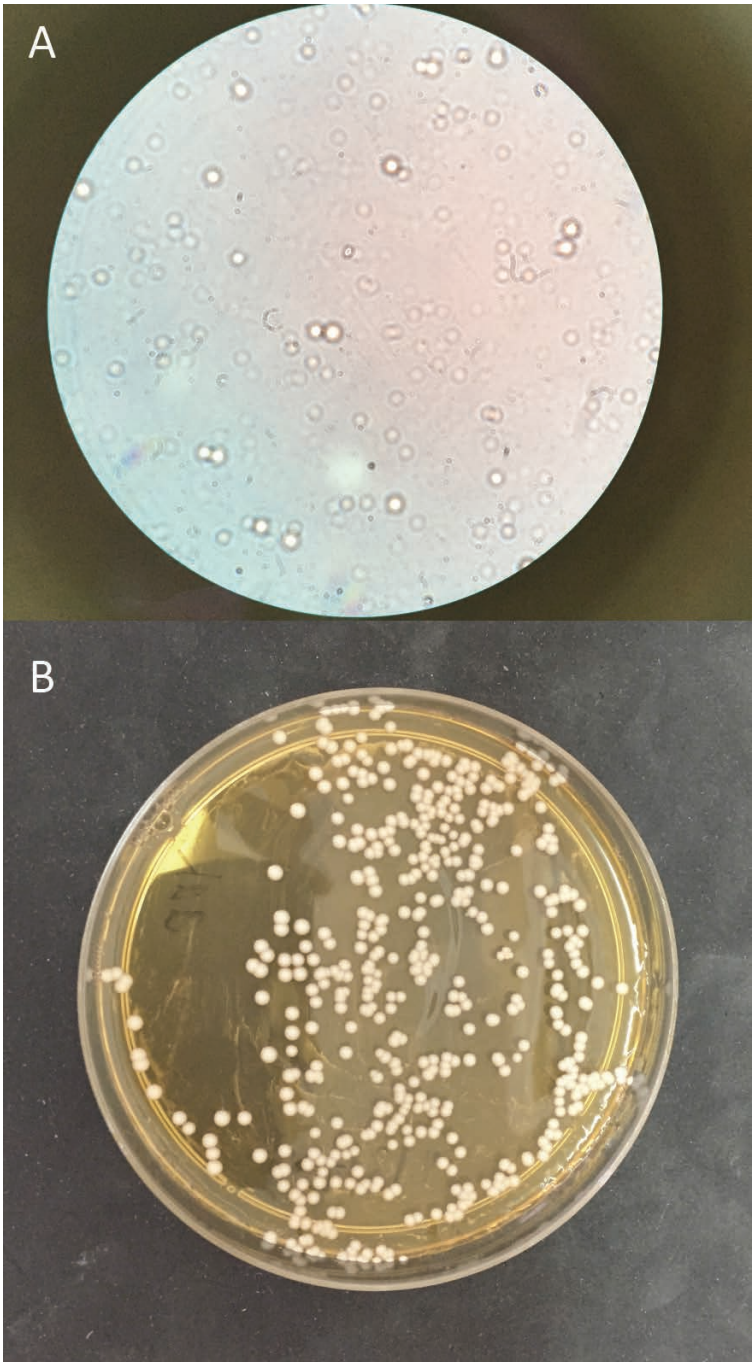

Figure 1. A) Indian Ink staining of cerebrospinal fluid revealing encapsulated yeasts; B) growth of cream colonies from cerebrospinal fluid on YPD agar.

ly fungicidal drugs in combination with ICP control by LP followed by immune restoration with antiretroviral therapy (ART). There have been giant strides in ART rollout across Africa in recent years, leading to the prospect of long-term survival if patients can survive CM, provided ART is not commenced too early given the risk of IRIS.[19] However, access to manometers remains a significant problem as accurately measuring and managing pressure is crucial, although solutions such as substituting manometers with IV tubing may be feasible. Additionally, fluconazole monotherapy remains the only option in much of the African continent, despite its inferiority to Amphotericin B based regimens.

Our case shows how effective simply performing serial LPs for patients even with the most drastic complications of CM can be, yet also demonstrates the need to campaign for greater access to both manometers and antifungal drugs in these settings.

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