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Case Report

Managing intracranial pressure in HIV-associated cryptococcal meningitis saves Life: Case report of two patients admitted to a Tanzanian hospital

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Abbreviations AFB: Acid Fast Bacilli; ALT: Alanine Transferase; ART: Antiretroviral Therapy; CSF: Cerebral Spinal Fluid; FBP: Full Blood Picture; HIV: Human Immunodeficiency Virus; ICP: Intracranial Pressure; IV: Intravenous; LFT: Liver Function Test; MTB: Mycobacteria Tuberculosis; OD: Once a Day; OP: Opening Pressure; QID: 4times a day; RFT: Renal Function Test; SSA: Sub Saharan Africa

Abstract

Cryptococcal meningitis remains a major cause of HIV-related mortality worldwide with majority of cases occurring in sub Saharan Africa. Raised intracranial pressure is a common complication of cryptococcal meningitis and if left untreated is associated with irreversible blindness, deafness and other neurological and neurocognitive impairment. We present two cases which highlight the importance of therapeutic lumbar puncture in the management of raised intracranial pressure in HIV-associated cryptococcal meningitis.

Introduction

Cryptococcal meningitis remains a major cause of HIV-related mortality worldwide with majority of cases being residents of sub Saharan Africa (SSA) [1]. SSA accounts for 73% of the estimated cases of cryptococcal meningitis globally and contributes up to 75% of annual deaths [1]. Despite antifungal therapy mortality due to cryptococcal meningitis continues to remain high [2]. Raised intracranial pressure is a common complication of cryptococcal meningitis and if left untreated is associated with increased mortality. Additional complications accompanying cryptococcal meningitis with raised intracranial pressure include irreversible blindness, deafness and other neurological and neurocognitive impairment [3-5]. We present 2 cases of cryptococcal meningitis: one with very high fungal burden and initial normal opening pressure, and the other with hearing loss, reduced visual ability and bilateral VI cranial nerves palsies. These two cases highlight the importance of therapeutic lumbar puncture in the management of HIV-associated cryptococcal meningitis.

Cases Summary

Case 1

A 43 year-old man, newly diagnosed HIV positive was admitted at Mwananyamala Regional Referral Hospital due to severe headache, fever, seizures (generalized tonic-clonic), visual obscuration and vomiting for six days. On examination he was conscious (GCS 15/15), afebrile and no signs of meningeal irritation. The visual acuity was 0.200 for both left and right eyes. Brain CT scan was normal. Systemic examination was unremarkable.

Examination of Cerebrospinal Fluid (CSF) revealed clear fluid with an opening pressure (during admission) of 22cmH2O. Laboratory examination results for CSF were as follows: Indian Ink was positive, gram stain was negative, cryptococcal antigen was positive, quantitative fungal culture was 1,450,000 cfu/ml, CSF glucose was 3.2mmol/l, CSF protein was 240mg/dl, RBCs were 3/mm^3, and CSF WBC count2/mm^3.

The patient's CD4 count was 23/mm^3. Further laboratory analyses included full blood picture and creatinine were normal. The serum ALT was raised at 84U/L. A blood smear for Malaria parasite was negative and blood culture had growth of yeast cells. Chest X ray showed perihilar opacities and scattered reticulo-nodular opacities corresponding with pneumonia. Sputum for AFB and Gene Xpert for mycobacterium tuberculosis were negative.

Treatment for cryptococcal meningitis was initiated by giving oral fluconazole capsules 1200mg once daily and oralflucytosine 1200mg every 6 hours for two weeks. This was followed by oral

fluconazole 800mg daily for two weeks which was then reduced to 400mg once daily and continued for 6 weeks to complete 10 weeks of treatment. Injection ceftriaxone 2g IV OD for 7 days was given to this patient due to pneumonia. Antiretroviral therapy was delayed until when completed 4 weeks of antifungal therapy.

During the course of treatment serial therapeutic lumbar puncture was performed on days 3, 4, 7, 10, 14, 18, 19, 20, 22, week 4 visit, week 6 visit and week 10 visit. The corresponding opening pressures were 32, 9, 54, 19, 25, 67, 38, 50, 48, 16, 29 and 18cmH2O respectively. CSF was drained to maintain pressure at less ≤20 cmH2O (or half the opening pressure, whichever was higher). Approximately 10-20mls of CSF was removed when Opening Pressure (OP) was above 20cmH2O. The frequency of lumbar puncture was determined CSF pressure levels and by the symptoms of raised intracranial pressure presented by the patient (including headache, vomiting, and double vision).

Patient was discharged on day 15 after improvement but readmitted again on day 18 due to severe headache and vomiting. Lumbar puncture was done on re-admission and CSF OP was 67cmH2O. About 20mls of CSF was drawn during this procedure and patient reported a relief from headache. Quantitative fungal culture revealed 100cfu/ml, gram stain and CSF gene xpert were negative. As the fungal burden was decreasing compared to 120cfu/ml from CSF sample obtained on day 14 of treatment, patient continued with caps fluconazole 800mg once daily to complete two weeks and was kept under observation. He was discharged after improvement and instructed to attend follow up clinic. He was followed for 10 weeks. During week 4 follow up lumbar puncture was done CSF OP was 16cmH2O and quantitative fungal culture 30cfu/ml. On week 6, CSF OP was 29cmH2O and quantitative fungal culture 20cfu/ml. His last follow up visit was on week 10, CSF OP was 18cmH2O and had no growth on quantitative fungal culture. He was progressing well without symptoms of raised ICP and has improvement on his visual acuity 0.100 on both left and right eyes. Fluconazole dose was lowered to 200mg daily and patient was linked to HIV treatment clinic for follow up.

Case 2

A 27 years old male patient self-referral from home, known HIV positive since birth but not on ART. He presented with 7 days history of severe frontal throbbing headache and vomiting which was projectile being mostly comprised of recently eaten food. He also had high-grade fever, generalized tonic-clonic convulsions, blurred and double vision and hearing loss. He had no history of loss of consciousness. During admission he was conscious (GCS 15/15), afebrile (temperature 37.0 C), bilateral VI cranial nerve palsy, VIII cranial nerve palsy, and a visual acuity of 1.300 in both eyes. The rest of physical examination on the patient revealed no significant findings. Cryptococcal meningitis was suspected and lumbar puncture was done. The results revealed CSF OP of 95cmH20, Indian Ink was positive, cryptococcal antigen positive, quantitative fungal culture 220000 cfu/ml, CSF glucose was 1.7, CSF protein was 340mg/dl, CSF WBC 001/mm3 and RBCs 003/mm3. Furthermore laboratory analysis included a CD4 count of 60 cells/mm3.Full blood picture, creatinine and ALT were normal.

Treatment for cryptococcal meningitis was initiated. He received amphotericin B injection 49mg (calculated at 1mg/kg) daily and flucytosine tablets 1000mg (calculated at 100mg/kg/day) every 6 hours for 7 days. This was followed by fluconazole capsules 800mg orally once daily for two weeks, then lowered to 400mg daily for six weeks to complete 10 weeks of treatment. Antiretroviral therapy was initiated after completing 4 weeks of antifungal treatment.

During the course of treatment therapeutic lumbar puncture was done serially on day 2, 3, 4, 7, 9, 14, 15, 16, 17 and 18. The corresponding pressures were 56, 48, 29, 28, 27, 59, 38, 53, 40 and 33. CSF was drained 10-30mlsto maintain pressures levels to less or equal to 20cmH20 (or half the opening pressure). Follow up quantitative fungal culture on days 7 and 14 of treatment were 55,000 cfu/ml and 1,300 cfu/ml respectively. Patient showed marked improvement after 10 weeks of treatment. He had complete recovery of his hearing, improved vision with complete recovery of the left eye visual acuity 0.000 and marked improvement of the right eye with visual acuity 0.400. He had no symptoms of raised ICP. He was given capsules fluconazole 200mg oral once daily for secondary prophylaxis and linked to HIV treatment clinic for follow up.

Discussion

These cases highlight the importance of therapeutic lumbar puncture for the management of raised intracranial pressure in patients with HIV-associated cryptococcal meningitis. Intracranial pressure can build over time and any rise may initially be asymptomatic. Even in the absence of raised intracranial pressure, performing serial lumbar puncture helps remove the cryptococcal antigen [6]. It is important to bear in mind that even with normal opening pressure at baseline, patient should have a repeat lumbar puncture done as he might later develop raised ICP. Reducing a raised ICP by performing serial lumbar puncture has shown to improve survival, even in patients with high fungal burden. Strict adherence to serial therapeutic lumbar puncture speeds recovery of the cranial nerves palsies, hearing and vision loss caused by raised intracranial pressure [7]. Delay in ART initiation to these patients until after completing 4 weeks of antifungal therapy reduces the risk of IRIS. Other researchers found that deferring ART until after 4 weeks after the start of antifungal therapy improved survival rates among patients with cryptococcal meningitis [8].

Serial lumbar puncture has an important effect to the outcome of medical therapy. It has been demonstrated that elevated intracranial pressure at baseline is correlated with higher titres of cryptococcal antigen [9]. Patients with increased ICP are more likely to have positive Indian Ink smear and more severe clinical manifestations of the disease including headache, vomiting, papilledema, hearing loss, vision loss and neurological findings such as meningismus, cranial nerves palsies, confusion, altered mental status and coma. Severely raised ICP if not addressed increases 10 to 14-day mortality [9-11].

The use of drugs such as acetazolamide for the management of increased ICP in patients with crypotococcal meningitis is not effective [12]. Some studies have evaluated the use of adjunctive glucocorticoids therapy to treat cryptococcal meningitis. The largest study showed that patients who were treated with glucocorticoids had significantly worse outcomes compared with patients who did not receive glucocorticoids [9].

Serial lumbar puncture is often employed because this is the safest option (compared to lumbar drain or intraperitoneal shunt). Draining CSF not only remove fluid, it also restores auto regulatory reabsorption function of the villi. This is because the mechanism of raised ICP is primarily due to a failure of CSF reabsorption via the arachnoid villi caused by cryptococcal polysaccharide capsule [13].

The frequency of lumbar puncture must be determined by the symptoms of the patient and previous pressure levels. In sub Saharan Africa, insufficient attention has been given to raised ICP in patients with cryptococcal meningitis. Practical ICP management protocols are lacking and manometers are not easily available. ICP measurement with IV tubing sets may be a good alternative [14]. Several studies have highlighted that if not addressed increased intracranial pressure is associated with increased 10-14 day mortality in patients with cryptococcal meningitis [9-11]. One study showed that patients with normal opening pressure at baseline who did not receive a repeat therapeutic lumbar puncture had higher10- day mortality than those who had elevated opening pressure but underwent repeat lumbar puncture [15]. Tanzanian researchers found that strict adherence to serial lumbar punctures decreased 30-day mortality from 75% to 46% [14]. Even a single therapeutic lumbar puncture has been shown to reduce mortality in patients with cryptococcal meningitis [10]. Therefore, management of patient with cryptococcal meningitis should consist of baseline lumbar puncture and CSF drainage in case of elevated ICP exceeding 20cmH2O or when symptoms are consistent with elevated ICP. Daily lumbar punctures are important until when pressures have decreased or symptoms of raised ICP have resolved.

Conclusions

From the cases reported we suggest that immune compromised patients coming with headache, fever, vomiting, visual alterations and other neurological manifestations must be immediately investigated for cryptococcal meningitis. Early diagnosis of the disease, early initiation of appropriate antifungal therapy and management of raised intracranial pressure are key measures in achieving successful treatment of this infection.

Recommendations

Resource-appropriate practical guidelines for raised ICP management should be developed for sub Saharan Africa. Adoption of serial lumbar punctures for ICP monitoring and management in Africa would likely lead to a major reduction in HIV-related mortality.

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