Case Report

Cryptococcal meningitis in a none-HIV infected five month old infant with rickets: Case report

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Abstract

Crypotococcal is an invasive fungal disease, now endemic in the tropics. It is largely transmitted through inhalation, but can be transmitted locally through skin and eyes. Mostly, it causes disease in immune compromised individuals, especially older children and adults, where it causes disseminated disease.

Baby JG aged 5 months presented with a prodrome of respiratory symptoms. His anterior fontanel was wide and bulging, and had poor muscle tone. A week later, he developed convulsions, and a depressed sensorium. Haemogram showed a leucocytosis. Bone metabolism showed serum low phosphate and high alkaline phosphatase. Cerebrospinal fluid biochemistry was unremarkable, but microscopy was positive for Indian ink stain and crypotococcal antigen. HIV PCR test was negative. Clinical improvement was observed on institution of antimeningitic therapy, and intravenous fluconazole, vitamin D3 and calcium supplementation, but another spike was noted on day 7 of therapy. The findings of crypotococcal meningitis in HIV sero-negative infant is very rare. Immune reconstitution syndrome may occur during treatment.

High index of suspicion for cryptococcosis is needed in high risk children with sub-acute presentations of meningitis, and a relatively normal CSF cell counts and biochemistry. Routine fungal screening of CSF for all suspected children is justified.

Key words: Crytococcosis, Leucocytosis, Sero-negative, Antimeningitic

Introduction

Crytococcosis is an invasive fungal disease caused by a monomorphic encapsulated yeast. There are various variants, but *crytococcus neoformans var neoformans* is the commonest worldwide [1]. It is commonly found in soil, in avian droppings, on fruits and vegetables. *crytococcus neoformans var gatti* is mainly found in the tropics, where it causes endemic disease [2]. *Cryptococcus gattii* causes infections in immunocompetent people but *C. neoformans v. grubii*, and *v. neoformans* usually only cause clinically evident infections especially in persons with compromised immune system [3].

Seroprevalence studies show limited exposure in infants, but exposures occur in less than 5% in children over 5 years and 60% in adults [2-6]. The disease occurs in 5-10% of HIV infected adults, mainly when CD 4 counts fall below 200mm^3[7]. It also occurs in other forms of immune suppression such as those with malignancy, or on immune suppressants. Paediatric cases are evenly distributed among the immunocompromised and the immunocompetent individuals [4-6]. The disease is transmited mainly through inhalation, but can also be locally transmitted through the skin and eyes [3]. Pulmonary disease is the commonest site, but dissemination occurs in the immune compromised hosts to involve the brain, the meninges, skin, eyes, and the skeletal system. Lung disease presents with fever, cough, chest pain, and constitutional symptoms. Neurologic disease causes a sub-acute or chronic meningitis presenting with headaches, malaise, convulsions or altered mental status [3]. Sepsis syndrome may occur in the immunocompromised.

Case Presentation

JG was a 5 month old male child, born and raised in Nairobi, Kenya The mother reported complains of irritability, poor feeding, fever, nasal congestion, and cough for 7 days prior to admission. The child was initially seen in an outpatient clinic as case of respiratory tract infection and put on normal saline nose drops, amoxicillin, and paracetamol, but his condition remained poor. On the morning prior to admission, the child developed convulsions, and was brought back to hospital. This was the first episode of fits. The child was born SVD at term, in

hospital, had a birth weight of 3.5kg. Perinatal history was unremarkable. The mother was a housewife, and exclusively breastfed the child. The child's immunization was up to date. His growth chart revealed weight faltering in the previous two months. Findings on admission revealed a sick looking child, was febrile- 39^0C, weighed 5.8 kg, had some dehydration and mild pallor. On neurologic examination he was drowsy, hypotonic, and poorly responsive to pain. The anterior fontanelle was wide and bulging. The head circumference was 41cm. The neck was equivocal. The child had widened wrists, mild frontal boozing, and poor trunk support but no rickety rosary. In the respiratory system, he had tachypnoe of 56 breaths /min, had no chest retraction, but had bilateral transmitted sounds. He was mouth breathing with hypertrophied inferior turbinates, but had a normal throat exam. His abdomen was full, but not tender. The cardiovascular system was unremarkable.

The initial impression was meningitis in a child with rickets. A lumbar puncture done immediately was not under pressure. Cerebrospinal (CSF) fluid analysis revealed protein of 30g/dl, glucose of 160mg/dl, leucocytes 0-3phf, Gram stain and Zeehil Nelsen stains were negative, but the Indian ink stain and crypotococcal antigen (CRAG) test were positive. Blood slide for malaria was negative, on the haemogram done; leucocytosis of 900/mm^3, with a relative neutrophillia of 78%. Haemoglobin level was 9.7g/dl, microcytic hypochromic picture, Widal test -negative, a random blood sugar was 6.7mmol/l, blood urea nitrogen and electrolytes were normal, Liver Function Tests (LFTs) were normal except an elevated alkaline phosphatase of 502mmol/l, serum calcium was low at 1.15mmol/l, serum phosphorus was 1.85mmol/l, urinalysis was normal. Blood, CSF, and urine cultures were taken. X-ray of the wrists showed features of rickets. He was started on antimeningitic therapy with intravenous ceftriaxone, amikacin, and fluconazole. He was also put on phenobarbitone, paracetamol, calcium gluconate, vitamine D3 injection, betamethasone/ neomycin nose drops and cetrizine.

The fever dropped within 72 hours, but on day 7 of treatment, the child started spiking fever again. The culture reports back were all negative. A chest X-ray was ordered but the result was normal. Repeat white blood cell counts were normal, C-Reactive protein was 46mg/dl and the Erythrocyte Sedimentation Rate (ESR) was 26mm/hr. A CT scan of the head revealed a normal brain parenchyma and para-nasal sinuses. Human Immune Deficiency Virus (HIV) RNA PCR test was negative. Intravenous ampotericin B was added to his treatment for 14 days. Hydrocortisone injection was added to prevent inflammation caused by immune reconstitution reactions. Serial monitoring of electrolytes was done during treatment, and remained normal. The fevers gradually settled and the child clinically improved. A repeat lumbar puncture was done on day 28 of treatment and was negative for all stains including indian ink. CSF -CRAG was also negative. The child was discharged on oral fluconazole for up to 6 weeks, as well as oral calcium, iron and vitamin D supplements.

Discussion

Indian test result and the clinical manifestations in the child were indicative of cryptococcal infection. None the less, the finding of *cryptoccoccal meningitis* in HIV seronegative infant is very rare. However, this was documented in some studies previously [3,4]. Cryptoccocosis is rare, and especially in infants, but it does occur in 1% of HIV positive children. High prevalence was documented in children with immunocompromising conditions such as those with acute leukaemia, primary immunodeficiency, children on immune suppressive therapy, immunosuppression from rheumatic disorders, malnutrition, and celiac disease [4,6]. Pulmonary disease is commonest in immune competent individuals, and tends to be assymptomatic. Meningitis is the commonest presentation of disseminated disease [3]. This tends to be caused by *Cryptococcus neoformans var gratti*, a species which is found more commonly in the tropics [3]. The coincidental finding of rickets in this child may have contributed to some immune suppression, which then predisposed the child to the disseminated disease. In retrospect, the initial respiratory symptoms in this child may have been the pulmonary phase before progression to the meningitis. However this was not considered at that point. Detection of cryptococcal antigen (capsular material) by culture of CSF, sputum and urine provided definitive diagnosis [9]. Blood cultures may be positive in heavy infections. Indian ink of the CSF is a traditional microscopic method of diagnosis [10], although the sensitivity was poor in early infection, and may miss 15-20% of patients with culture-positive cryptococcal meningitis [11]. Cryptococcal antigen from CSF is the best test for diagnosis of cryptococcal meningitis in terms of sensitivity [12]. However, species isolation was also not done in this case.

Routine screening for HIV infected patients with meningitis is advised [13]. Serial lumbar punctures may have been useful for monitoring [12,13]. Standard therapy remains a combination of intravenous amphotericin B and either fluconanazole or flucytosine for 2 weeks, then followed with oral flucozole for 8-10 weeks [9,15,16].

The Immune Reconstitution Inflammatory Syndrome (IRIS) was described in immunocompetent hosts with meningitis caused by *C. gattii* and *C. grubii*. Several weeks or even months into appropriate treatment, there was sudden onset deterioration with worsening meningitis symptoms and progression or development of new neurological symptoms. IRIS was however much more common in immune-compromised hosts (25% versus 8%). In severe IRIS cases, treatment with systemic corticosteroids was utilized.

Mortality rate from cryptococcal meningitis is about 15% - 30% in developed countries, but may rise

up to 70% in low income countries [3]. Mortality rates are higher in HIV infected patients, who have relapse rates of more than 50% but was reported to be unusual in adequately treated in non-HIV infected patients. However, neurologic sequelae such as hydrocephalus, deafness, cranial nerve palsies, visual defects, seizures, ataxia are common.

Conclusion

Cryptoccoccal meningitis in HIV sero-negative infant was diagosed in a 5 month infant whose initial impression was like meningitis in a child with rickets. Clinicians must have a high index of suspicion for cryptococcossis, especially when patients have sub-acute or chronic presentations of meningitis, relatively normal CSF cell biochemistry, and poor response to initial course of antibiotics. In view of high prevalence of high risk children including the malnourished, preterms and HIV infected children in our settings, routine screening of CSF for all suspected children is justified.

Conflict of interest: Authors declare that we have no conflict of interest.

Acknowledgement

To Jamma Mission Hospital administration, where the case was managed. The study received no funding.

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