Cryptococcal meningitis in an immunocompetent child

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Introduction

Cryptococcus is a fungus that is found in the soil[1]. The most serious infections develop in patients with defective cell-mediated immunity such as acquired immune deficiency syndrome, organ transplantation, reticuloendothelial malignancy, corticosteroid or other immune modulatory treatment or with sarcoidosis[2]. In healthy people, the fungus usually does not cause serious illness because of immune system's ability to counter infection[2]. Rare cases of cryptococcal meningitis in immunocompetent patients have been reported[3], but in most, have been related to frequent exposure to avian droppings[4]. We report a child without immune deficiency or other risk factors, who suffered and subsequently recovered from a relapsing cryptococcal meningitis.

Case Report

A 4-year old girl presented with acute onset of fever, severe headache and vomiting for 6 days on a background of chronic mild headache for 1 year and visual impairment for 6 months. Examination revealed significant neck stiffness, and bilateral papilloedema. Her peripheral blood counts revealed a moderately elevated white blood cell (WBC) count of 18,000/cu mm with 60% neutrophils, C-reactive protein (CRP) of 80mg/L and an erythrocyte sedimentation rate (ESR) of 110mm during the first three weeks of therapy. Neuro-imaging (computed tomography scan and magnetic resonance imaging) showed widespread meningeal enhancement and presence of dilated ventricles.

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This was initially drained using an extra dural drain followed by insertion of a ventriculo-peritoneal shunt. Cerebrospinal fluid (CSF) examination revealed an increase in both polymorphs (54 cells/mm^3) and lymphocytes (138 cells/mm^3), lymphocytes predominating. Protein in CSF was 240g/dl, and sugar was unrecordable. Gram stain was negative for bacteria and CSF did not detect bacterial antigens or tuberculosis (negative AFB, GeneXpert and culture on Lowenstein Jensen medium). Indian ink staining of CSF detected hyphae and CSF was positive for cryptococcal antigens. Later, cryptococci were cultured from CSF.

She was treated with a protracted course of intravenous amphotericin B therapy and intravenous fluconazole resulting in slow improvement. After 12 weeks of intravenous therapy in the consolidation phase, oral fluconazole was given for 9 months. Several complications, including non-communicating hydrocephalus requiring shunt insertion, complete loss of vision in right eye (no perception of light) with later development of optic nerve atrophy and reduced acuity in the left (6/36), and significant motor regression, were experienced resulting in three months of hospital stay. There was no direct evidence of fungal infection affecting the eye.

Before completion of maintenance therapy, she presented again with features of raised intracranial pressure fever and drowsiness. Elevated cryptococcal antigen count in the CSF required a second course of antifungals with intravenous voricanazole and fluconazole. She was maintained on a longer course of maintenance therapy with oral flucytosine.

She has had serial assessments of cryptococcal cell counts, cryptococcal antigens, sugar and protein assessments in CSF, initially frequently, but later monthly, and subsequently six monthly. The very slow improvement of sugar level (mmol/L) with decrease of fungal load (cryptococcal cell count/ high power field) are described in Figure 1. No cryptococcal antigens have been detected over the past 5 years and she has remained off medications for more than 4 years now.

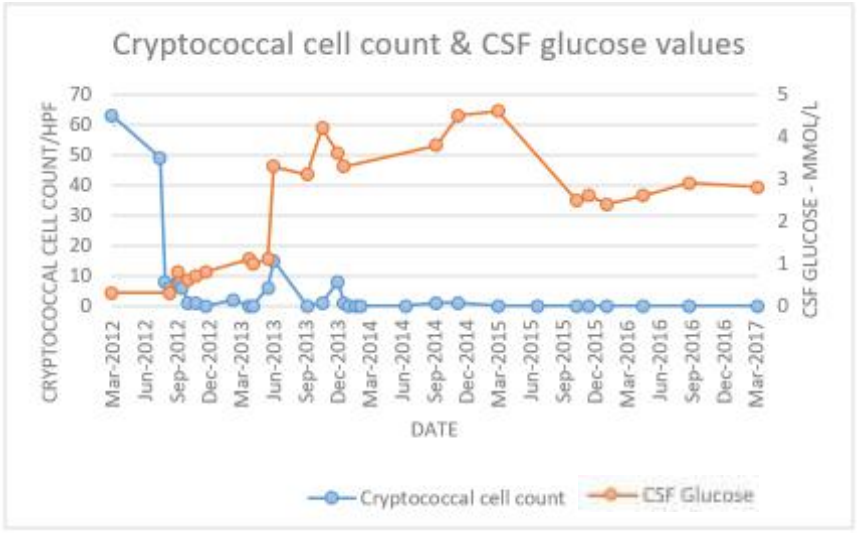

Figure 1: ***Cryptococcal cell count and CSF glucose values***

Now at 10 years of age she remains symptom free for over four years. She was tested negative for acquired immune deficiency and also negative for primary immune deficiency (PID). These included evaluation of serum immunoglobulin levels, complement levels, nitroblue tetrazolium test and flow cytometry for CD 3, 4, 8 and 19 cell counts. All these have shown normal results. With these findings, the PIDs such as CD4 Deficiency and X linked hyper IGM syndrome are excluded. The rare possibilities of autosomal dominant GATA2 deficiency or auto-antibodies to GMCSF or INF γ are not excluded but in these very rare conditions cryptococcal meningitis has not been identified. Currently, she is well except complete loss of vision in the right eye and shows good school performance as a grade 5 student.

Discussion

This case highlights cryptococcal meningits as a cause of chronic meningitis even in an immunocompetent child. Unlike previous reports[3,4] of this in those with apparently normal immune system, this girl had no exposure to avians or frequent play with soil.

Cryptococcosis is a systemic disease mainly reported in adults with compromised immunity[1]. Cases of cryptococcal disease have been reported in children less frequently, compared to those of adults with compromised immunity[5]. Cryptococcus is usually found in the soil and also in some bird excreta[1,2]. Cryptococcus gattii, more common in tropical, subtropical and temperate regions[6] has been reported in some of the recent documentation of cryptococcal meningitis in immunocompetent patients[5,7]; however, they often remain symptom free of systemic illness, often localized to the respiratory system only[6].

The commonest presentation of systemic cryptococcosis is with neuro-cryptococcosis, presenting as meningitis in close to 85%[6]. Headache is the commonest symptom reported in these patients in 78%[6]. Other symptoms and signs include fever (65%), nausea and vomiting (45%), confusion and meningeal signs in 35%[6,8]. Visual impairment is also reported as a presenting symptom[8]. Our patient experienced all these main clinical features and had compatible imaging findings. The visual loss in our patient is probably due to the fungal infection as well as the high dose of amphotericin. One of the striking observations in this case was the identification of zero levels of sugar in the cerebrospinal fluids. This was very slow to show improvement with therapy, however, it steadily improved to normal CSF sugar levels over time with appropriate treatment with antifungals.

Previous normal health, complete resolution of fungal load, absence of any further illness for over 5 years, negative screening for immune deficiency confirmed this girl to have suffered from systemic cryptococcosis in spite of immunocompetence.

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