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Intracerebral Cryptococcosis presenting as intractable headache

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Abstract
Acute meningoencephalitis presenting with seizure and altered sensorium is a common presentation seen in tropical countries like India, etiology of which ranges from bacterial, viral, fungal or mycobacterial meningoencephalitis. However, such sinister and life threatening diagnosis is seldom expected in patients who are stable and present to Out Patient Department (OPD) with only a single complaint of headache. We report a 39 year old man who presented with headache and was diagnosed with intracranial cryptococcosis with no cause of immunosuppression.

Keywords: cryptococcosis, headache, intracranial, immunocompetent

Introduction
Intracranial cryptococcosis is a common opportunistic infection in HIV positive patients especially at CD4 count less than 200 cells/mm [3]. Unusually, it can manifest as the first acute onset symptom complex in those with severe immunosuppression and can be the first presentation of the underlying disease. We report such a case of a patient who presented with headache, was radiologically suspected to be having cryptococcosis, and was subsequently diagnosed for the same and responded to treatment.

Case Report
A 39yr old man, resident of a village in India presented with complaints of headache for 2 weeks. Headache was diffuse, non-pulsating and not relived by over the counter medications. Patient had no history of vomiting, cough associated sputum production, hemoptysis or chest pain. There was no loss of weight or loss of appetite in the past. There was no history of alcohol consumption, Diabetes mellitus, malignancy, and history of chemotherapy or any other immuno- suppressive medications. There was no history of blood transfusion in past, promiscuity or any intravenous drug abuse. The patient had received oral and parenteral analgesics from another hospital for 7 days with no symptomatic benefit.
On examination, the patient was oriented to time, place and person with Glasgow coma scale score of 15. He was afebrile with pulse rate was – 78/minute regular, Blood Pressure was – 110/72 mm of Hg and his Respiratory Rate was – 20 breaths /min. Pallor was present and there was no cyanosis, icterus or clubbing.
Patient had normal deep tendon reflexes with no neck rigidity. Pupils were normal reactive with no evidence of papilledema. He had bilateral equal air entry in the chest. Cardiovascular examination was normal. The blood investigations of the patient are summarized in Table 1 which revealed normal leucocyte count and normal liver and kidney function tests.
Cerebrospinal fluid (CSF) analysis (Table 2) was suggestive of normal cytology, with slightly raised proteins with normal ADA and no AFB and organisms seen. CSF was analysed for PCP by giemsa and silver stain, cryptococcal meningitis by India ink, toxoplasma by serology, tuberculosis by CBNAAT and MGIT culture, and bacterial culture for pyogenic organisms but all the above tests turned out negative. Hepatitis B and C, malaria serology, dengue, chikungunya, scrub typhus serology all were negative. Chest x-ray and USG abdomen were normal.
A neurology opinion was taken and MRI brain was adviced. The MRI (figure 1 to 11) was suggestive of characteristic finding suggestive of intracranial cryptococcosis- multiple discrete and confluent hyper intensities in bilateral caudate nucleus, putamen, globus pallidus and periventricular white matter of bilateral fronto-parietal regions. The periventricular spread was suggested by few hyper intense areas closely abutting the sulcul spaces. Subsequently, the CD4 count was reported 18cells/mm3 suggestive of severe immunosuppression. HIV-1 and 2 test by ELISA was negative twice and there was no atypical cells on peripheral smear of blood.
Patient was started on injection amphoterecin B and patient improved clinically. Patient is currently on maintenance fluconazole and planned for a fresh CD4 count analysis. Also in subsequent follow up, CSF sent for fungal culture showed positive growth in SDA medium confirming the diagnosis of cryptococcosis.

Table 1: Hematological and Microbiological investigations

	Value
Hemoglobin (gram %)	10.8
TLC (Total leucocyte count/mm3)	11000
DLC (differential leucocyte count)	80 % polymorphs
	19% lymphocytes
Platelet count	2.7 LAC
B. UREA (mg/dl)	24
S. Creat	0.2
Sodium	142
Potassium	4.3
T. Bilirubin	0.4
AST/ALT/ALP	23/32/68
INR	1.1

Table 2: Special Investigations

HIV-1(ELISA)	**Positive**	**CSF- ADA**	**2 IU/L**
HepB HepC	negative	CSF-India INK	Negative
Malaria Dengue chikungunya	negative	CSF- CBNAAT MGIT Culture	Negative
CSF – Cytology Sugar Protien	NO Pus Cell 59 mg% 60 mg%	CSF for PCP Stain	negative

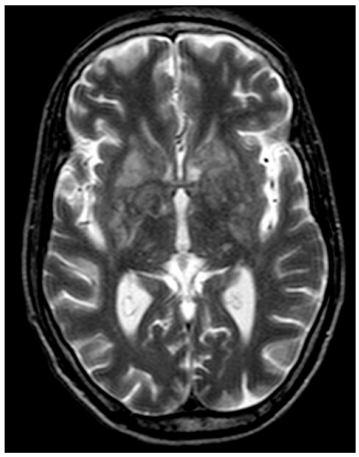

Fig 1: Multiple T2 hyper intensities are seen in bilateral caudate nuclei, putamen, and globus pallidus

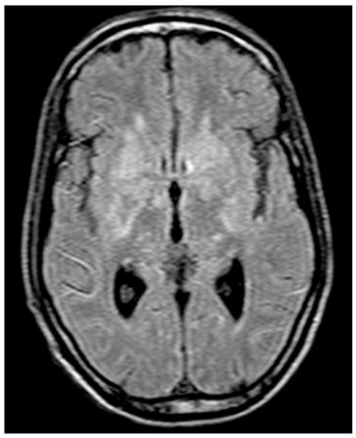

Fig 2: Multiple FLAIR hyper intensities are seen in bilateral caudate nuclei, putamen, and globus pallidus

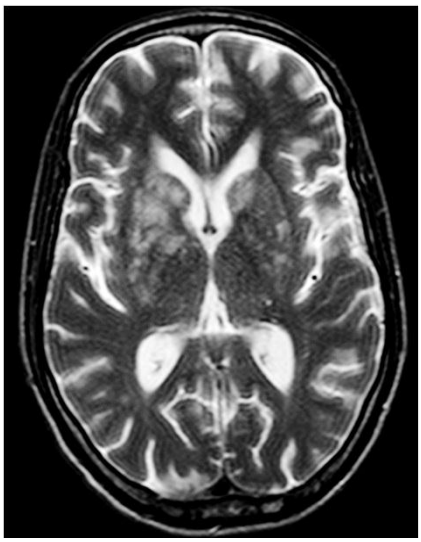

Fig 3: Multiple T2 hyper intensities are seen in bilateral caudate nuclei, putamen, and globus pallidus

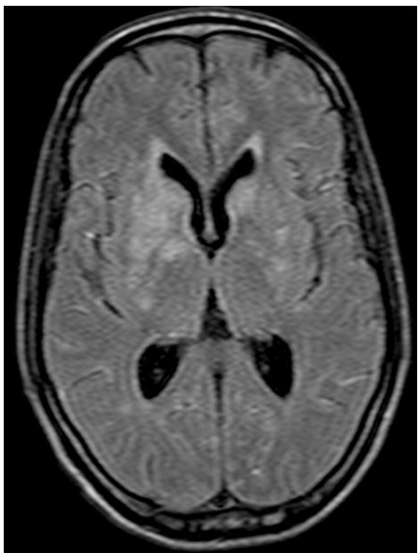

Fig 4: Multiple FLAIR hyper intensities are seen in bilateral caudate nuclei, putamen, and globus pallidus

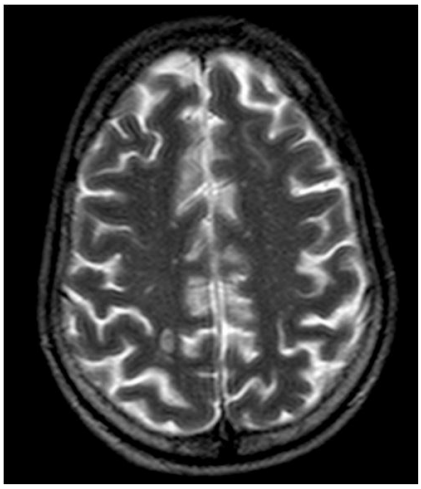

Fig 5: Multiple T2 hyper intensities are seen in bilateral centrum semi vale

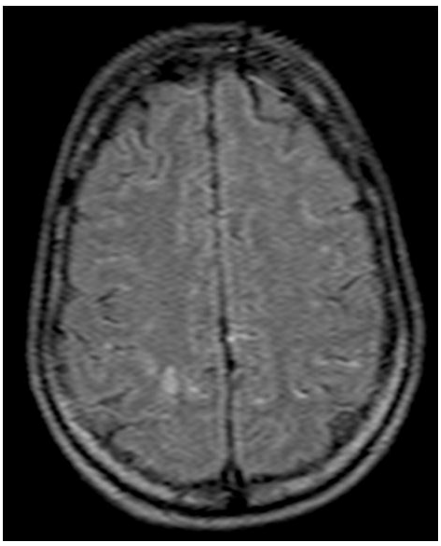

Fig 6: Multiple FLAIR hyper intensities are seen in bilateral centrum semi vale

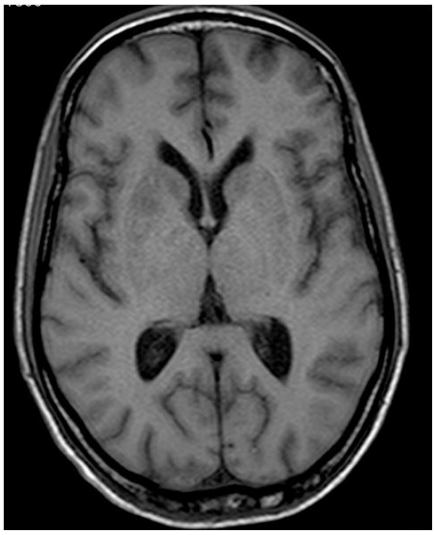

Fig 7: The lesions are non-enhancing on post contrast scan

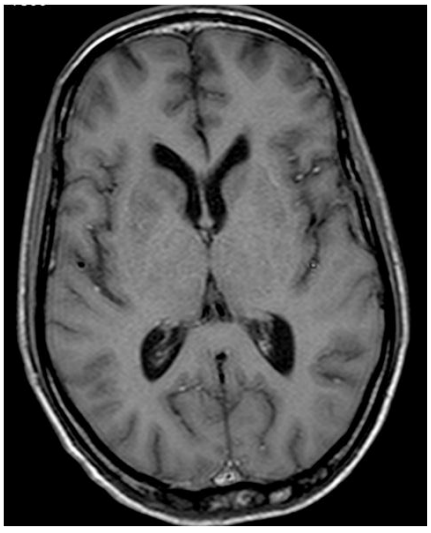

Fig 8: The lesions are non-enhancing on post contrast scan

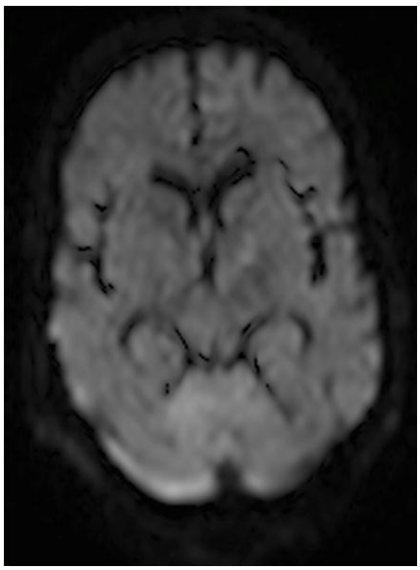

Fig 9: No restriction on Diffusion weighted imaging

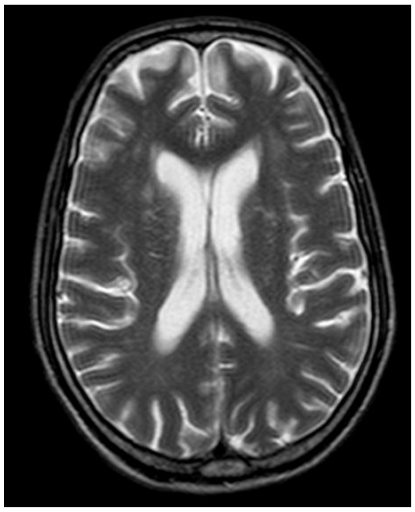

Fig 10: Multiple T2 hyper intensities are seen in bilateral periventricular white matter

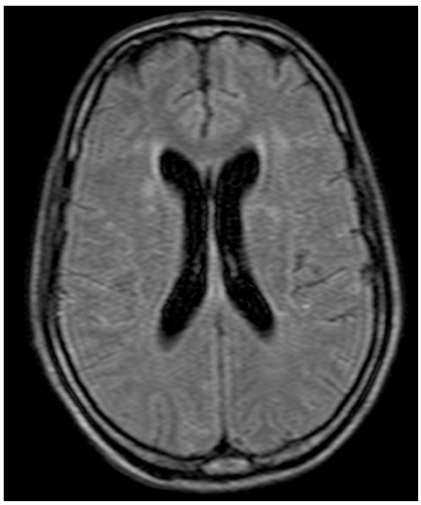

Fig 11: Multiple FLAIR hyper intensities are seen in bilateral periventricular white matter

Discussion

C. neoformans is ubiquitous in nature, yet the incidence of cryptococcosis is relatively low as it possesses low virulence [1]. Infection in the host is kept under control with no manifestation of symptoms by active cell mediated immunity but when immunity wanes as in HIV infection, virulence factors like the polysaccharide capsule act to produce disease and spread it hematogenously to extra pulmonary tissues. They usually spread in neurological tissue to cause meningoencephalitis which can be fatal if left untreated [2, 3].

In the past, cryptococcosis was a rare infection and as many as a third of all patients gave history of steroid use. The numbers steadily increased with the advent of HIV pandemic, it is the third most common cause of central nervous system infection after tuberculosis and toxoplasma [4, 5]. It may be, uncommonly the first manifestation of HIV.[6] More than three fourths of the cases associated with AIDS develop when the CD4 T-lymphocyte count falls below 50 cells/μL [7].

Abnormal cerebrospinal fluid (CSF) findings, such as pleocytosis, low glucose concentrations, and high protein concentrations, are seen in approximately 40% of patients with AIDS-related cryptococcal meningitis. In the review by Darras-Joly *et al*, 26% of HIV-positive patients presenting with cryptococcal meningitis had normal CSF findings; this is consistent with previous reports in the literature. Therefore, findings of an apparently normal CSF should not exclude the possibility of cryptococcal infection [8].

India ink and cryptococcal antigen in CSF have very high sensitivity to detect cryptococcal infection. India ink was negative in our patient and antigen testing was not available at our centre. One of the reasons of negative India ink can also be predominant encephalitis without clinical or radiological meningitis in the patient.

Literature also states that CSF sample is negative for cryptococcal antigen assay in very early in the disease or in those with very high titers due to prozone effect and in certain patients with cryptococcosis [9] A positive fungal culture, however, is the gold standard for diagnosis of cryptococcal infection and CSF samples shows fungal growth in almost all the cases. Fungal cultures also help to determine the species of the infecting organism and sensitivities to various antifungal agents [10].

In our patient, radiology helped in clinching the diagnosis which was later confirmed by culture. Tubercular meningoencephalitis typically present with basal exudates with meningeal enhancement and hydrocephalus. All these were absent in our patient and CSF was also negative for ADA, Gene Xpert. The imaging findings of cryptococcosis may consist of meningoencephalitis, intraventricular or intraparenchymal cryptococcosis, gelatinous pseudocysts, or hydrocephalus. Cryptococcus may spread along the perivascular spaces from the basilar cisterns, which was typically seen in the MRI of our patient, and cryptococcal infection may appear on images as rapidly growing, none nhancing "cysts." Dilated perivascular spaces resulting from the presence of gelatinous pseudocysts are a frequent finding, and their presence in an immunocompromised patient should raise a red flag [11]. The most common sites for cryptococcosis are the basal ganglia, thalamus, and cerebellum [12]. The main differential diagnoses for an enhancing lesion in the basal ganglia are cryptococcosis, lymphoma, toxoplasmosis, and, to a lesser extent, pyogenic abscess. In view of negative toxoplasma antibody, normal peripheral smear, unavailability of cytospin analysis and MR-spectrometry and negative pyogenic cultures, a diagnosis of cryptococcosis was suspected and patient was given amphotericin. Our patient had a dramatic improvement and was discharged after 2 weeks of therapy on oral fluconazole and ART.

Thus to conclude, clinical examination, radiology and laboratory investigations, all have to be correlated to arrive at a diagnosis. Even though rare, intracranial cryptococcosis with no objective evidence of meningitis can be the initial presentation of severely immunocompromised non- HIV infected patients. A high index of suspicion should be kept for such diagnosis to start prompt treatment so as to prevent mortality.

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