

Cryptococcal infections in children can be associated with a myriad of primary immunodeficiency diseases – our experience at Chandigarh, North India

Cryptococcal infections have been described in children with certain immune deficient states like Human Immunodeficiency Virus infection, diabetes mellitus and malignancies. We describe here 4 cases who had cryptococcal infections and search for underlying immune defect led to the finding of a myriad of primary immunodeficiencies in some of them.

Case 1: 3 year girl, symptomatic since 6 months of age in form of recurrent pneumonia, otitis media and oral thrush, failure to gain weight and height, now presented with history of cough, fever and respiratory distress. On examination, she was severely malnourished, had tachypnea (RR- 60/min), clubbing, oral thrush and diffuse crepitations on auscultation over chest. Investigations revealed anemia (hemoglobin 76gm/L), CT guided fine needle aspiration cytology (FNAC) from lung showed *Cryptococcus* sp. Search for immune deficiency was carried out. Immunoglobulin G was elevated (2.2 gm%) with CD3 (57%), CD20 (15.7%) and CD56 (27.3%) being within normal limits. Further evaluation uncovered the presence of CD4 lymphocytopenia (CD4+ T cells: 5.7% and absolute CD4+ T cell count of 274 cells/mm³). Search for causes of CD4 lymphocytopenia was unremarkable and a diagnosis of idiopathic CD4 lymphocytopenia was concluded.

Case 2: 3 year boy, presented with fever and pain abdomen for 3 months. Had jaundice 1 month back. Examination revealed generalized lymphadenopathy, jaundice and hepatomegaly. Investigations showed anemia, conjugated hyperbilirubinemia with elevated alkaline phosphatase and gamma glutamyl transferase. Biopsy from axillary lymph node revealed multiple necrotizing granulomas with numerous refractile fungal yeasts in the giant cells, histiocytes and in the necrotic tissue confirming to the morphology of *Cryptococcus*. A diagnosis of disseminated cryptococcosis was made. Evaluation for underlying immune defect revealed elevated serum immunoglobulin E (>10,000 U/L) with reduced Th17 cells (0.9% as compared to 2.1% in age matched control) and p-STAT3 (10.9% as compared to 30.8% in control).

Case 3: 4 year boy, presented with fever, rash and pain abdomen for 6 weeks. Examination showed cervical and axillary lymphadenopathy, hepatosplenomegaly and discrete umblicated lesions over trunk and limbs. FNAC from cervical lymph node showed granulomatous inflammation and numerous intracellular and extracellular round to oval capsulated organisms consistent with *Cryptococcus*. Search for immune deficiency was unrewarding. With a diagnosis of disseminated cryptococcosis, Amphotericin B and flu cytosine are initiated. On follow-up, skin lesions were healing and organomegaly disappeared.

Case 4: 4 year boy, presented with fever, headache, seizures and altered sensorium for 1 month. Investigations: Ultrasonography of abdomen showed altered echo texture of liver with multiple hypo-dense lesions in spleen. Cerebro-spinal fluid (CSF) examination showed *Cryptococcus* on India-ink staining. CSF as well as blood culture revealed *Cryptococcus neoformans*. A diagnosis of disseminated cryptococcosis was arrived at. Evaluation for underlying immune defect showed reduced expression of IL12R β 1 on lymphocytes(10.0% as compared to 46.4% in age matched control). This was one of the uncommon cases of disseminated cryptococcal infection with IL12R β 1 defect.

Cryptococcal infections including disseminated cryptococcal infections have been reported in immunocompetent children (1,2). However, these children should not be termed as immunocompetent only because no apparent immunodeficiency could be demonstrated in them. At best, these children may be called as “apparently immunocompetent”.

Case No.	Age	Sex	Presentation	Cryptococcal infection proved by	Underlying Immune defect
1	3 yrs	F	Recurrent pneumonia, failure to thrive, oral thrush	CT guided FNAC lung	Idiopathic CD4 lymphopenia

2	3 yrs	M	Fever, pain abdomen, generalized lymphadenopathy, conjugated hyperbilirubinemia	Lymph node biopsy	Elevated IgE (>10,000 U/L), reduced Th17 cells (0.9% as compared to 2.1% in age matched control) and p-STAT3 (10.9% as compared to 30.8% in control)
3	4 yrs	M	Fever, rash, lymphadenopathy, hepatosplenomegaly	Lymph node biopsy	No obvious defect
4	4 yrs	M	Fever, headache, seizures, altered sensorium	CSF india ink, blood and CSF culture	IL12R β 1

1. Saeed N, Ansari HA, Khan N, Aijaz M. Disseminated cryptococcosis in an immunocompetent child. *BMJ Case Rep.* 2016 Nov 16;2016

2. Jain BB, Bose D, Mondal R, Chattopadhyay S. Disseminated Cryptococcosis in an Immunocompetent Child. *Turk Patoloji Derg.* 2017;33(1):77-80