CASE REPORT

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME IN NON HIV CHILDREN ON ANTI TUBERCULAR TREATMENT: A CASE SERIES

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ABSTRACT: Immune reconstitution inflammatory syndrome (IRIS) in a patient on anti-tubercular treatment (ATT) in the setting of antiretroviral therapy (ART) is well described, but it is not as common in non-HIV patients. Distinguishing this paradoxical reaction (PR) from disease progression or treatment failure is an important issue in CNS tuberculosis management. Thus one must keep a watch for neurological deterioration in a child with CNS TB. We are presenting a case series of three non HIV children who developed TB-IRIS while on anti-tubercular drugs, who subsequently responded to steroids along with continuation of ATT.

KEYWORDS: Immune reconstitution, Inflammatory syndrome.

INTRODUCTION: Paradoxical reactions (PR) are defined as transient worsening or appearance of new signs or symptoms or radiographic manifestations of tuberculosis that occur after initiation of treatment and are not the result of treatment failure.¹

Tuberculosis-associated IRIS can present as one of two main syndromes: paradoxical reaction after the start of ART in patients receiving tuberculosis treatment (“Paradoxical” tuberculosis-associated IRIS) or a new presentation of tuberculosis that is “unmasked” in the weeks following initiation of ART (“unmasking” tuberculosis associated IRIS).² Paradoxical reaction can develop in a non HIV infected individual on ATT due to restoration of immune function.³

The time of onset of PR is defined as the number of days from the start of treatment to the commencement of deterioration. The median duration of PR is two-three months⁴,⁵

Paradoxical neurologic TB-IRIS accounts for 12% of paradoxical TB-IRIS cases.⁶ Neurologic TB-IRIS include new or recurrent neurologic symptoms and signs like headache, focal neurologic deficits, nuchal rigidity, confusion, seizures, cerebellar signs, cognitive impairment or psychiatric manifestations.⁵,⁷

We are reporting three cases of non HIV children with CNS tuberculosis developing PR after start of ATT.

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CASE 1: A 6yrs old boy presented with history of fever of 8 days & 1 episode of generalized tonic clonic convulsions on day 8 of fever. The child was admitted in a private hospital, diagnosed & treated as bacterial meningitis. In view of persisting meningeal signs and fever despite of appropriate treatment, child was re-evaluated, repeat CSF analysis was suggestive of TB meningitis (Sugar-35,protein-380,LDH-32,cells-50 all lymphocytes) CT brain & chest x-ray were
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normal, Mantoux test was negative, and child was put on ATT and steroids. Child showed improvement was discharged on ATT.

After 14 days of ATT, child again developed neck stiffness and fever, hence child was referred to our hospital. On evaluation child had signs suggestive of meningitis with left-sided facial nerve weakness. MRI brain showed ring enhancing lesions with perilesional oedema scattered over cerebrum, cerebellum and brain stem with extensive leptomeningial, patchy meningeal involvement and tiny enhancing lesions were also seen in spinal cord at C7 & D2 vertebra. HIV status was negative. A diagnosis of TB-IRIS was considered & Dexamethasone was started then changed to prednisolone given for 4 weeks along with continuation of ATT. He showed improvement and was discharged.

CASE 2: A 14yr old female child presented with, history of headache of 10days, vomiting of 2 days. On evaluation child was found to have severe anaemia with cervical lymphadenitis & papilledema without meningeal signs. Child was investigated and found to have severe iron deficiency anaemia (Hb-6, serum iron-13, TIBC-520, UIBC-507, Transferin saturation-26) mantoux test was positive, FNAC of cervical lymph nodes (Granulomatous lymphadenitis) & CSF analysis were suggestive of tuberculosis (sugar-57, protein-267, LDH-22, cells-6 all lymphocytes), CT brain suggestive of raised intracranial tension features. Sputum for acid fast bacilli (AFB), CXC was normal & HIV status was negative. Child was started on ATT along with steroids for 4 weeks, with the diagnosis of TB meningitis. 45 days after discharge child came with severe headache, neck rigidity, MRI brain was normal. Probability of treatment failure or IRIS was considered and child was started on steroids, mannitol & ATT was continued. With treatment child improved.

CASE 3: A 15yrs old boy with history of pulmonary TB in father 16yrs back, presented with 1 episode of left focal convulsion. On evaluation HIV test, Mantoux test was negative. Chest x-ray was normal. MRI brain showed conglomerate ring enhancing lesions in both occipital lobes with perilesional oedema & a ring enhancing lesion in right frontal lobe, with perilesional edema. CSF analysis was normal (Sugar-100, protein-6, LDH-23, Cells-0) Child was diagnosed as Tuberculoma brain & started on ATT along with prednisolone & carbamazepine.
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After two months child had two breakthrough convulsions associated with headache, & vomiting. MRI brain showed increase in size of lesion in the right frontal lobe with perilesional edema. MR spectroscopy showed lipid lactate peak. TB-IRIS was considered & steroid was started, given for 4 weeks tapered & stopped.

After completion of 9 months course of ATT, repeat MRI brain showed decrease in the size of lesion. There were no neurological deficits.

DISCUSSION: Immune Reconstitution Inflammatory Syndrome (IRIS) is a heightened inflammatory response to a pathogen in the setting of immunologic recovery after immunosuppression. It occurs in those who have undergone a reconstitution of the immune responses against an antigen. It is an exuberant and dysregulated inflammatory response to invading microorganisms: It manifest when an abrupt shift of host immunity from an anti-inflammatory and immunocompromised status towards a pathogenic proinflammatory state, occurs as a result of rapid decrease or removal of factors promoting immunosuppression or initiating inflammation.

An acute exacerbation of Th1 responses against mycobacterial antigens appear to cause IRIS in patients co-infected with HIV &TB.

In addition to HIV, IRIS has also been observed in solid organ transplant recipients, women during post-partum period, neutropenic patients, tumour necrosis factor antagonist recipient.

The cause of the PR in immunocompetent person can be attributable to several factors like persistence of lipid rich insoluble cell wall antigen, exposure & release of new antigen targets during mycobacterial killing, hypersensitivity to tuberculoprotein & exaggerated immune restoration following TB induced immunosuppression.

Antitubercular drug resistance should be excluded in all cases of suspected TB-IRIS and corticosteroids should be used with caution for patients with presumed TB-IRIS until the results of drug susceptibility testing is known.
Though it is important to distinguish TB-IRIS from other causes like inadequate drug regime & multidrug resistant TB, distinguishing IRIS from clinical deterioration due to ongoing immunodeficiency is ill defined and controversial in paediatric population.13

Majority of patients with IRIS have a self-limiting disease course. Mortality associated with IRIS is relatively uncommon.14

In the present study there were three children with CNS tuberculosis, all were immunocompetent, all of them developed PR between 14 to 45 days after commencement of ATT.

One of our patients had spinal intramedullary tuberculoma, cerebellar, pontine tuberculoma with facial nerve palsy, which is rare.15

These reactions can be effectively managed with continuation of ATT along with systemic corticosteroids.

REFERENCES:
1. Burman W J, Jones B E. Treatment of HIV related Tuberculosis in the era of effective antiretroviral therapy. Am J Respir Crit Care Med Vol. 164. Pp. 7–12, 2001 Internet address: www.atsjournals.org.
2. Immune Reconstitution Inflammation Syndrome Case Definition Version. Iris Case Definitions (Revised 01/1/09), http://actgnetwork.org/IRIS_case_Definitions.
3. Martin Blondel G. Curr Op Infect Dis. 2012; 25 312-320.
4. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. Antivir Ther. 2005; 10(3): 417-22.
5. Burman W,Weis S,Vernon A, Khan A, Benator D,Jones B, Silva C,King B LaHart C, Mangura B, Weiner M, El-Sadr W. Frequency, severity and duration of immune reconstitution events in HIV-related tuberculosis. Int J Tuberc Lung Dis. 2007 Dec; 11(12): 1282-9.
6. Pepper DJ, Marais S, Maartens G, Rebe K, Chelsea, Meintjes G. Neurologic Manifestations Of Paradoxical Tuberculosis- Associated Immune Reconstitution Inflammatory Syndrome. Clin Infect Dis. 2009; 48 (11): e96-e107.
7. Graeme Meintjes, Stephen D Lawn, Fabio Scano, Gary Maartens, Martyn A French, William Worodria et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis. 2008 Aug; 8(8): 516–523.
8. KE Elizabeth and K Jubin Immune Reconstitution Inflammatory Syndrome in CNS Tuberculosis. Indian Pediatr 2014;51: 668-670
9. Sun HY, Singh N. Immune reconstitution inflammatory syndrome in non-HIV immunocompromised patients. Curr Opin Infect Dis. 2009 Aug; 22(4): 394-402. doi: 10.1097/QCO.0b013e32832d7aff.
10. Anne Bourgarita, b, Guislaine Carcelaina, Valerie Martinezia, Caroline Lascouxxb, Veronique Delceyc, Brigitte Gicqueld, Eric Vicaute, Philippe H. Lagrangef, Daniel Serenib and Brigitte. Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected. AIDS 2006, Vol. 20 No 2.
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11. Anirban Das, Sibes Kumar Das, Abhijit Mandal, and Arup Kumar Halder. Cerebral tuberculoma as a manifestation of paradoxical reaction in patients with pulmonary and extrapulmonary tuberculosis. J Neurosci Rural Pract. 2012 Sep-Dec; 3(3): 350–354.
12. Meintjes G, Rangaka MX, Maartens G, Rebe K, Morroni C, Pepper DJ, Wilkinson KA, Wilkinson RJ. Novel relationship between tuberculosis immune reconstitution inflammatory syndrome and antitubercular drug resistance. Clin Infect Dis. 2009 Mar 1; 48(5): 667-76.
13. Judy Orikiiriza, Sabrina Bakeera-Kitaka, Victor Musiime, Edison A. Mworoz, Peter Mugyenyi, and David R. Boulware. The clinical pattern, prevalence, and factors associated with immune reconstitution inflammatory syndrome in Ugandan children. AIDS. 2010 Aug 24; 24(13): 2009–2017.
14. Surendra K. Sharma and Manish Soneja. HIV & immune reconstitution inflammatory syndrome (IRIS). Indian J Med Res. 2011 Dec; 134(6): 866–877.
15. Das K K, Jaiswal S, Shukla M, Srivastava A K, Behari S, and Raj Concurrent cerebellar and cervical intramedullary tuberculoma: Paradoxical response on antitubercular chemotherapy and need for surgery. J Pediatr Neurosci. 2014 May-Aug; 9(2): 162–165.

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