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Recurrent Salmonellosis in a Child with Complete IL-12R β 1 Deficiency

Mohammad Faizan Zahid¹, Syed Asad Ali², Fyezah Jehan², Abdul Gaffar Billo², Jean-Laurent Casanova^{3,4,5}, Jacinta Bustamante^{4,5,6}, Stephanie Boisson-Dupuis^{3,4,5}, and Fatima Mir^{2,*}

¹Medical College, Aga Khan University, Karachi 74800, Pakistan

²Department of Pediatrics and Child Health, Aga Khan University, Karachi 74800, Pakistan

³St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, New York, 10065, USA

⁴Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U980, Necker Enfants Malades Hospital, Paris, 75015, France, EU

⁵University Paris Descartes, Imagine Institute, Paris, 75015, France, EU

⁶Center for the Study of Primary Immunodeficiencies, Assistance Publique–Hôpitaux de Paris, Necker Enfants Malades Hospital, Paris, 75015, France, EU

Abstract

A 3 year old boy presented with fever, abdominal pain and cervical lymphadenopathy. He had previously been treated empirically with anti-tuberculous therapy twice, at age 9 months and 27 months, for peripheral lymphadenopathy. An older sibling died of suspected tuberculous meningitis.

Mantoux test was normal. Bone marrow and lymph node biopsy ruled out lymphoma and absolute neutrophil and lymphocyte counts were normal. Blood and lymph node cultures were positive for *Salmonella typhi*. The child's symptoms resolved with IV ceftriaxone and he was discharged.

Over the next 2 years, the child was admitted every 2–3 months for culture positive *S. typhi* bacteremia with complaints of fever, abdominal distention and dysentery. HIV workup was negative. A prolonged course of probenidol and high dose amoxicillin increased interval between episodes to 4–5 months only. Cholecystectomy was debated and deferred due to suspicion of immunodeficiency. Blood samples from patient and parents were sent to France for workup and IL-12R β 1 deficiency was found. Parental counseling and subsequent patient management remained difficult in view of financial constraints and outstation residence of family. At age 7 years, the child presented with small bowel obstruction. He was managed conservatively with antibiotics, IV fluids and blood transfusions, but eventually succumbed to endotoxic shock. This case highlights the importance of considering IL-12R β 1 deficiency in children with repeated

salmonellosis, a diagnosis which precludes intensive and aggressive monitoring and management of the patient in scenarios where bone marrow transplants are not feasible.

Introduction

Interleukin-12 (IL-12), an immune-modulating cytokine produced by activated antigen presenting cells (macrophages and dendritic cells) plays an important role in combating infections with intracellular organisms. It induces interferon gamma (IFN- γ) production in T and Natural killer (NK) cells and promotes T helper cell (T_H cells) activity. In children with mutations in the interleukin-12 receptor β 1 (IL-12R β 1) gene, lymphocytes have an impaired response to IL-12 and display an impaired production of IFN- γ [1]. These patients are extremely susceptible to infections with mycobacteria (even poorly virulent *Bacillus Calmette–Guérin* (BCG) vaccines and environmental nontuberculous mycobacteria) and *Salmonella* species [2]. Organisms other than intracellular pathogens rarely cause clinical disease in such patients. Though most reports so far show favorable survival, we report the case of a child with IL-12R β 1 deficiency and recurrent salmonella bacteremia who eventually succumbed to toxic mega-colon and septic shock.

Case Summary

A 3 years old male child presented with intermittent fever for one and a half years associated with lympho-nodular swellings (cervical), abdominal pain, blood in stool and intermittent rash on face and scalp. Physical examination revealed tachycardia (120 beats per minute), generalized lymphadenopathy, peripheral edema and tinea faciei and capitis.

In past medical history, generalized lymphadenopathy and intermittent fever had been noticed first at age 9 months. He had received an empiric anti-tuberculosis therapy (ATT) regimen twice, once at the age of 9 months and later at the age of 27 months. As per parental recall, he had received BCG vaccine at birth, Hepatitis B, DPT and OPV at 6, 10 and 14 weeks and measles vaccine at 9 months as per national expanded program on immunization (EPI) schedule from Pakistan. BCG scar was not present. The parents had a consanguineous marriage. Of three siblings, two were living. The oldest, a 12 year old brother was well, the second, a 9 year old sister was underweight with conductive deafness due to bilateral chronic suppurative otitis media (CSOM). The third sibling had succumbed to a fatal case of meningitis a year back at age 4 years (suspicion of TB meningitis was solely based on lymphocytic pleocytosis alone in CSF). This child had also had recurrent episodes of blood in stool and a history suggestive of scrofula at 3 years of age. There was no history of contact with an adult with Tuberculosis. All siblings excluding the oldest had received at least two empiric 3 drug ATT regimens for 6–9 months due to generalized lymphadenopathy. All children had received BCG vaccination at birth as per EPI schedule.

Initial differentials at the time of presentation included miliary tuberculosis, lymphoma and primary immunodeficiency syndrome. Laboratory investigations showed borderline Mantoux test (10mm), normal tumor lysis workup (serum electrolytes, BUN, creatinine, phosphate, uric acid and lactate dehydrogenase) and normal immune workup

(immunoglobulin levels, Nitrobluetetrazolium test, CD4/CD8 cell ratio and HIV antibody titers).

Complete blood count (CBC) showed neutrophilia. Remaining investigations, which included clotting profile, liver function tests (LFTs) and electrolytes were within normal limits.

Abdominal ultrasound and chest x-ray showed enlarged paraaortic, mesenteric and hilar lymph nodes. Lymph node biopsy done in his local province was reviewed. Histopathology showed hemophagocytic lymphohistiocytosis (HLH). This was attributed to be infection-associated. Mycobacterial infection was suspected but empiric regimens were deferred.

The child returned to the hospital after a month with high grade fever and discharging, ulcerated pre-auricular and submandibular lymph nodes. Pus and blood cultures yielded *Salmonella typhi*, sensitive to amoxicillin and ceftriaxone and resistant to ciprofloxacin. Fungal and acid fast bacilli (AFB) cultures showed no growth. He was managed with IV ceftriaxone for 2 weeks and discharged.

Over the course of 3 subsequent years he had multiple in-patient and out-patient visits with complaints of fever, abdominal distention and loose stools with blood. Blood cultures were sent at the onset of most febrile episodes and revealed amoxicillin and ceftriaxone sensitive *Salmonella typhi* which responded to 2 weeks of the antibiotic. Probenecid and amoxicillin prophylaxis proved successful in delaying the episodes but was not tolerated well beyond 8 weeks.

Elective cholecystectomy was considered but deferred after abdominal ultrasound revealed a normal gall bladder. After repeated episodes of salmonellosis over one and a half year, the possibility of a defect in the IL-12/IFN γ pathway was considered. Samples were sent for work up to the Laboratory of Human Genetics at Necker Medical School in France. A homozygous nucleotide substitution (1791+2T->G) was found on two base pairs after the end of exon 15, by sequencing all the coding and flanking intron sequencing of IL-12R β 1. This mutation has already been described in other patients with Mendelian susceptibility to mycobacterial disease (MSMD, MIM 209950 syndrome)[3, 4] and leads to a complete IL-12R β 1 deficiency without expression of the receptor on the cell surface membrane. In our patient, the result of the mutation was a frame-shift leading to a stop codon, and the non-expression of the protein on the cell surface membrane. Over the subsequent year, he continued to present with febrile episodes associated with abdominal distention and loose blood containing stools within 1–2 weeks of completing a 2-week ceftriaxone course for a prior febrile episode. Cultures were only sent intermittently due to financial constraints.

Complications in the form of sub-acute small bowel obstruction became apparent by end of the fifth year of illness. Abdominal CT scan showed a soft tissue mass involving the caecum, ascending colon and appendix, causing mass effect and proximal small bowel obstruction. Diffuse circumferential thickening of rectosigmoid portion was also noted, along with abdominal lymphadenopathy, hepato-splenomegaly and a deposit in the left adrenal gland. Mucosa-associated lymphoid tissue (MALT) lymphoma was suspected. An endoscopic biopsy was considered to rule out MALT lymphoma but was deferred due to the

friable nature of the gut. Resection of bowel and stoma formation was considered to relieve the obstruction as a last resort, however the family withdrew consent to the high risk procedure. After 3 weeks of conservative management with antibiotics, IV fluids and blood products, the child eventually decompensated and passed away.

Discussion

Mutations in the IL-12R β 1 gene have been described before, which result in absent cellular responses to IL-12, and consequent lack of production of IFN- γ due to absence of the IL-12R β 1 receptor on the surface of T_H cells and NK cells [1, 2, 5, 6]. IL-12R β 1 deficiency is the most common genetic cause of MSMD syndrome [7,8]. Patients with this genetic defect are extremely susceptible to infections by intracellular pathogens such as environmental nontuberculous mycobacteria (NTM), *Salmonella* species, and even BCG vaccines [2,9,10]. They are also susceptible to the more virulent *Mycobacterium tuberculosis* [11]. The exploration of the response to BCG+IL-12 (and BCG+IFN- γ as a control) was performed for this patient. No IFN- γ production could be detected in response to BCG+IL-12 in the patient. This could be attributed to the complete IL-12R β 1 deficiency as reported earlier [3,4]. However the test was inconclusive as another possible reason for the absent response could be destruction of T_H cells and NK cells during the shipping time of the blood from source to the laboratory (4–5 days). Our patient experienced possible BCG or TB disease in the first few years of life followed by recurrent tinea capitis and multiple episodes of *Salmonella* bacteremia caused by *Salmonella typhi*. Systemic terbinafine relieved the tinea capitis, recurrence of which was largely attributed to selective pressure of repeated broad spectrum antibiotic use. Disseminated and local candidiasis has been more typically associated with these defects [12].

Case reports describe IL-12R β 1 deficiency in patients with repeated *Salmonella* infections [8,10,11,13–15]. Staretz-Haham et al. [10] described a patient with *Salmonella* bacteremia who was mostly treated with ceftriaxone like our patient. Ozen et al. [8] successfully eradicated carrier status using a prolonged course of ciprofloxacin followed by trimethoprim-sulfamethoxazole (cotrimoxazole) prophylaxis. Monotherapy with ceftriaxone or combination therapy with ceftriaxone and ciprofloxacin have been the mainstay of treatment in most cases of recurrent salmonellosis reported in literature [8,10,13]. In some instances of recurrent salmonellosis, antibiotics along with prolonged prophylaxis have been associated with clinical success [2,8,10], in others with or without BCG disease where therapy with antibiotics alone was not sufficient to relieve symptoms of septicemia, administration of IFN- γ resulted in rapid defervescence and resolution of symptoms [13,16–19].

Our patient was treated with ceftriaxone on all occasions of symptomatic septicemia. Interferon may have been a useful adjunct to antimicrobial therapy in his case. A higher fatality has been associated with complete IL-12R β 1 deficiency than cases of partial deficiencies [20].

A review of 141 patients from 102 kindreds in 30 countries [7] showed mean age at first infection of 2.5 years and a higher mortality of 32% among symptomatic patients compared

to the 15% reported in a 41 patient series [4]. Cause of death was predominantly BCGosis followed by environmental mycobacteria, tuberculosis and salmonellosis (predominantly non-typhoidal). Though development of mycobacterial disease years after an uneventful BCG vaccination has been reported in one patient [5], most case reports [15,21] describe IL-12R β 1 deficient patients who have experienced BCG disease shortly after being inoculated with BCG vaccine. It has been suggested that IL-12 or IL-23 component deficiency through IFN- γ independent pathways is strongly associated with salmonella disease while those with IFN- γ component deficiencies commonly present with mycobacterial disease [22,23].

De Beaucoudrey et al. [7] reported that clinical outcome of IL-12 deficiency was directly related to the therapeutic approach used. IL-12R β 1 deficient individuals were commonly treated with prolonged courses of antibiotics and exogenous interferon. Some underwent surgical resection of infected organs. In very rare cases, hematopoietic stem cell transplantation was carried out. Treatment options have not been evaluated due to lack of comprehensive data.

In conclusion, the suspicion of IL-12R β 1 deficiency should arise in children suffering from recurrent salmonella or mycobacterial infections. We recommend aggressive therapy with appropriate antibiotics, propitious use of interferon adjunctive therapy in moderate to severely ill children, and possibly bone marrow transplantation as a last resort. Long term antibiotic prophylaxis should be implemented for prevention of recurrent salmonellosis. Surgical resection of infected organs such as lymph nodes, gall bladder etc. can also be an option. Though cotrimoxazole, a combination of trimethoprim and sulfamethoxazole, has been used for long term prophylaxis to prevent septicemia in such patients with considerable results, it is not advisable due to high cotrimoxazole resistance among *Salmonella* species in our region [24,25]. We recommend the combination of amoxicillin and adjuvants like probenecid as a better alternative for antimicrobial prophylaxis in patients with IL-12R β 1 deficiency and recurrent salmonellosis. Interferon therapy should be given in patients not improving on antimicrobials alone (Table 1).

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Table 1

Clinical features of patients with defect in IL-12Rβ1 / IFNγ pathway suffering from recurrent salmonellosis reported in literature.

Reference	Gender	Parent's consanguinity	Age of onset	Organism isolated	Treatment		Status on last follow up and outcome	Defect in IL-12Rβ1 / IFNγ pathway	
					Septicemia	Prophylaxis		Age at diagnosis	Mutation
[10]	M	Yes	12 months	Group D <i>Salmonella</i> species	Ceftriaxone	Ceftriaxone / ciprofloxacin	Alive, responded well to prophylaxis	Not specified	In-frame large deletion encompassing exons 8-13 in the <i>IL-12RB1</i> gene
[8]	F	Yes	2 years 6 months	<i>Salmonella enteridis</i>	Ceftriaxone and ciprofloxacin	Cotrimoxazole	Alive, responded well to prophylaxis	2 years 7.5 months	Missense mutation with homozygous 670C4T substitution in the <i>IL-12RB1</i> gene
[13]	M	Yes	1.5 years	Group D <i>Salmonella</i> species	Ciprofloxacin and cefuroxime	Cotrimoxazole	Alive, responded well to prophylaxis	2 years	Homozygous mutation, skipping of exon 5 in the RNA and a frame shift and premature stop codon in the protein.
[13]	M	Yes	5 years	Group D <i>Salmonella</i> species	Ciprofloxacin	Cotrimoxazole	Alive, responded well to prophylaxis but had recurrence after stopping prophylaxis	6 years	r.783 + 1G>A resulting in aberrant splicing of the RNA and forming premature stop codons
[13]	M	Yes	5 years	<i>Salmonella enteridis</i> , <i>S. paratyphi</i> and <i>S. typhi</i>	Ciprofloxacin, cephalosporins and ampicillin/subactam (poor response) and then IFN-γ added (good response)	Yes but antibiotics not specified	Alive, responded well to prophylaxis except for occasional recurrences	13 years	Homozygous r.518G>C mutation resulting in the protein in the missense mutation R173P.
[27]	F	Yes	1 year 10 months	<i>Salmonella enteridis</i>	Ceftriaxone	None mentioned	Alive and had only 1 recurrence up until last follow up	4 years 2 months	Homozygous mutation in intron 8 (783+1G>A), exon 5 and 8 were missing in part of transcripts.
[15]	F	Yes	12 years	<i>Salmonella enteridis</i>	antibiotics (not specified) and excision of submandibular lymph nodes	None mentioned	Doing well, had an uneventful, successful pregnancy	Not specified	Homozygous r.518G>C mutation was detected, leading to an R173P missense mutation in the protein.

Reference	Gender	Parent's consanguinity	Age of onset	Organism isolated	Treatment		Status on last follow up and outcome	Defect in IL-12Rβ1 / IFNγ pathway	
					Septicemia	Prophylaxis		Age at diagnosis	Mutation
[17]	F	Yes	3.5 years	<i>Salmonella enteridis</i>	Corrimoxazole (poor response) and then IFN-γ added (good response)	Corrimoxazole and IFN-γ	Alive on last follow up (age 8 years), responded well to prophylaxis but had recurrence after stopping IFN-γ	Not specified	Deletion of 4.4 kb encompassing two coding exons in <i>IL-12P40 gene</i> .