Case Report

Recurrent *Salmonella* Bacteremia in Interleukin-12 Receptor β1 Deficiency

by Metehan Ozen,[a] Mehmet Ceyhan,[b] Ozden Sanal,[c] Mehmet Bayraktar,[d] *and* Lütfiye Mesci[e]
[a]*Inonu University, Faculty of Medicine, Division of Pediatric Infectious Disease, Malatya, Turkey*
[b]*Hacettepe University, Faculty of Medicine, Unit of Pediatric Infectious Disease, Ankara, Turkey*
[c]*Hacettepe University, Faculty of Medicine, Unit of Pediatric Immunology, Ankara, Turkey*
[d]*Inonu University, Faculty of Medicine, Department of Clinical Microbiology, Malatya, Turkey*
[e]*Hacettepe University, Faculty of Medicine, Unit of Pediatric Immunology, Ankara, Turkey*

Summary

Interleukin-12 receptor β1 (IL12RB1) deficiency causes vulnerability to poorly virulent mycobacteria and nontyphoid *Salmonella* species. We describe a 2.5 year-old girl with IL12RB1 deficiency, caused by a homozygous mutation in this gene, who presented with recurrent bacteremia caused by *Salmonella spp*.

Introduction

The major effector mechanism of cell-mediated immunity against intracellular pathogens is activation of infected macrophages by interferon-gamma (IFN-γ). IFN-γ production is up-regulated by interleukin-12 (IL12) [1]. Recently a new syndrome designated as 'Mendelian susceptibility to mycobacterial disease (MIM 209950)' was reported regarding IL12-IFN-γ axis [2]. This syndrome predisposes to a clinical disease caused by mycobacterial species even with weakly virulent strains. Most familial cases suggest autosomal recessive heredity, but the syndrome also segregates in an autosomal dominant [3] or X-linked recessive [4] pattern in some families.

IL12 pathway is also involved in protection against *Salmonella* species and less than half of the subjects experience nontyphoid salmonellosis. However, isolated salmonellosis is relatively rare in children with IL12 receptor β1 (IL12RB1) deficiency. We, herewith, describe a child who presented with isolated and recurrent *Salmonella* bacteremia due to IL12RB1 deficiency.

Case report

A 2.5-year-old girl was admitted with fever, diarrhea and vomiting for 2 days. She was born from a third-degree consanguineous marriage as a first child. Immunizations were up-to-date including BCG vaccine.

Stool examination showed more than 10 leukocytes per high-magnification field but no erythrocytes. Ceftriaxone therapy was commenced after obtaining samples for stool and blood culture. These cultures yielded growth of *Salmonella spp* which was susceptible to chloramphenicol, ceftriaxone and levofloxacine. She was discharged with oral cefixime on the 4th day to complete a total of 7-days course.

She had no complaints at the follow-up visit, but her blood and stool cultures yielded *Salmonella spp* again. She received parenteral ceftriaxone therapy for 10 days. One week after discharge, she was re-admitted with the complaints of fever and diarrhea. Lymphocyte subsets, serum immunoglobulin levels and complement markers were all within normal limits. Both blood and stool cultures obtained on re-admission yielded *Salmonella spp* with the same antibiogram results as in previous isolates. She received cefotaxime for 14 days. Blood and stool isolates, obtained on each occasion, were sent to Refik Saydam Hygiene Center in Ankara for serotyping. They informed us that they all are *Salmonella enterica* (serotype *enteridis*).

She came back for follow-up after 5 days, and *Salmonella spp* was again isolated on her both blood and stool cultures. She was transferred to Hacettepe Children's Hospital in Ankara for pediatric immunology consultation. Her routine immunological

Correspondence: Metehan Ozen, Ozalper Mah, Yasam Sitesi, C-Blok, No: 8, Malatya, Turkey.
E-mail <metehanoz@yahoo.com>.

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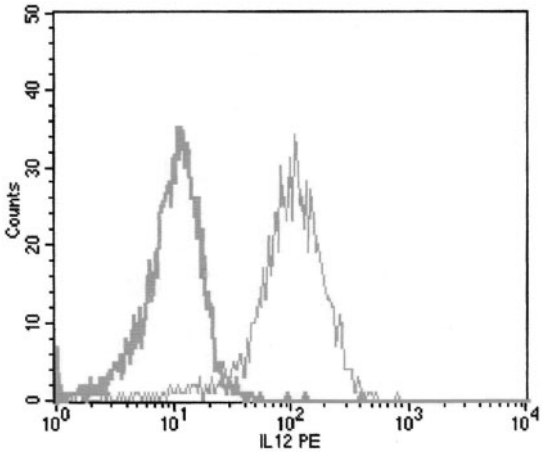

FIG. 1. IL-12RB1-FACS figure of the control.

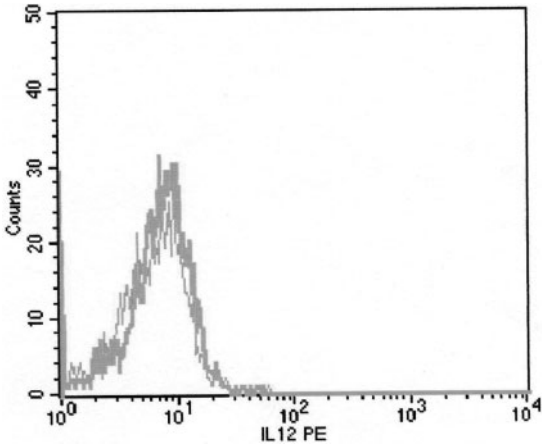

FIG. 2. IL-12RB1-FACS figure of the patient.

work-up showed no pathologic result in this institution. However, IL12RB-1 expression could not be observed in phytohemagglutinin-driven T cell blasts (Figs 1, 2). Furthermore, genetic analysis showed a missense mutation with homozygous 670C>T substitution in the IL12RB1 gene, where arginine is replaced by tryptophane, resulting in R175W. The patient was finally diagnosed as IL12RB1 deficiency. After receiving one month of quinolone therapy, she was assigned to trimethoprim-sulfamethoxazole prophylaxis. Her follow-up cultures did not yield *Salmonella* growth on any occasion for 9 months.

Her chest X-ray and family screening were within normal limits for *Mycobacterium tuberculosis*. Early gastric aspirates obtained thricely were negative for *M. tuberculosis* according to ARB, PCR and culture results. As her PPD test provoked 20 mm response, she received 2-drugs antituberculosis therapy, isoniazide and rifampin for 9 months. The parents were strictly advised to avoid the second dose of BCG vaccine.

Discussion

IL12RB1 deficiency is the most common genetic etiology of MIM 209950 syndrome. There are only 54 patients in the literature [5]. The majority of these subjects are diagnosed with the clinical manifestations of mycobacterial disease and/or previous history of tuberculosis.

Until now, only 5 patients have been reported to experience isolated salmonellosis. Staretz-Haham, *et al*. described a subject who had six episodes of asymptomatic *Salmonella* bacteremia caused by the same serovar [6]. He was treated with ceftriaxone on all occasions except for the last one in which ciprofloxacin was applied for 6 weeks. Similarly, our patient had 4 episodes of *Salmonella* bacteremia within 1.5 months and was treated with third generation cephalosporins for 7–10–14 days, consecutively. In the fourth and last period, we administered ciprofloxacin for 4 weeks, and afterwards trimethoprim-sulfamethoxazole for prophylaxis. After a follow-up of 9 months, her blood and stool cultures did not yield *Salmonella* spp on any follow-up visit. Therefore, we would like to emphasize the use of aggressive therapy with quinolones for long period in the successfull eradication of nontyphoidal *Salmonella spp*. In addition, prophylaxis with antibacterial drugs is needed to prevent recurrences.

As these subjects, with any type of underlying genetic defect, are highly vulnerable to *M tuberculosis*, we evaluated the patient and the family for tuberculosis. Her PPD test showed a large enduration of 20 mm. In a recent report from Spain; a female patient, sibling of a family with IL12Rb1 deficiency [7], developed pulmonary tuberculosis despite receipt of isoniazid prophylaxis for 3 months although isolate in the index case was reported to be sensitive. Therefore, two-drug antituberculosis chemotherapy was preferred even in the absence of active tuberculosis infection. The patient did not develop active infection after 9 months of follow-up on this regimen. As a result, single agent for short course may not be enough in the management of latent tuberculosis infection in this syndrome.

Even though BCG dissemination may occasionally result death in this syndrome [8], patients with an IL12R deficiency generally form a granuloma in response to this vaccine with no further complications. Our patient received BCG vaccine during the second month of life and had no complication. This is not surprising, since only about half of the patients described previously had non-tuberculosis mycobacterial infection, which suggests variability in the penetrance of IL12RB1 deficiency [9, 10]. However, the family was strictly advised to avoid the

second dose, which is routinely performed in the first year of primary school in Turkey, for a probable complication.

In conclusion, diagnosis of IL12RB1 deficiency should be contemplated for children with recurrent Salmonellosis. Aggressive and long-term antibiotic therapy should be used to eradicate *Salmonella spp* in this syndrome. We strongly recommend complete evaluation of subjects for Mycobacterial infection even in the absence of clinical manifestations.

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