Interleukin-12 Receptor β1
Deficiency Presenting as Recurrent Salmonella Infection

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We describe a child with interleukin-12 receptor β1 (IL-12Rβ1) deficiency caused by a homozygous IL12RB1 large deletion who presented at the age of 1 year with recurrent, often asymptomatic episodes of bacteremia caused by group D Salmonella species. No mycobacterial disease or other unusual infection was present. The episodes of salmonellosis were caused by an identical serovar during a period of 18 months. This is the first case of inherited IL-12Rβ1 deficiency diagnosed after isolated, recurrent salmonellosis.

Salmonella is a gram-negative bacillus that may cause asymptomatic infections in both an acute and a chronic form in immunocompetent individuals [1]. Symptomatic infections with this pathogen include acute gastroenteritis (both with and without local suppuration), bacteremia, infection with extraintestinal foci, and enteric fever. Specific serotypes are more commonly associated with certain clinical syndromes. Salmonella enterica serotype Typhi and S. enterica serotype Paratyphi A, B, and C cause enteric fever. Of the nontyphoid Salmonella species, S. enterica serotype Typhimurium causes acute intestinal infection, at times without symptoms; acute gastroenteritis is the most common clinical presentation [1]. S. enterica serotype Cholerasuis is commonly isolated from blood specimens, because this serotype rapidly invades the bloodstream with little or no intestinal involvement. Asymptomatic infections are usually identified via cultures of stool samples obtained during epidemiological investigations. Bacteremia, however, can occur with any Salmonella strain, especially in individuals with reduced host defenses [2].

Because Salmonella species very promptly cross the intestinal mucosal membrane and invade intestinal epithelial cells, they are relatively protected from the humoral immune system. They can behave like both extracellular and intracellular pathogens, and impaired host reticuloendothelial or cellular immune responses are important pathogenetic factors leading to bacteremia and dissemination of the pathogen. Children with primary immunodeficiencies, such as chronic granulomatous disease [3], hypogammaglobulinemia [4], DiGeorge syndrome [5], and complement C2 deficiency [6], are prone to recurrent Salmonella infections. Patients with secondary immunodeficiency caused by HIV infection [7], malnutrition [8], systemic lupus erythematosus [8], hematological and nonhematological tumors [9], organ transplantation [10], use of immunosuppressive drugs [8, 9], diabetes mellitus [9], and inflammatory bowel disease [11] are at increased risk. Children with sickle cell disease are prone to Salmonella septicemia and osteomyelitis [12]. Chronic infection is also associated with cholelithiasis [13], thalassemia [8], and Schistosoma infestation [14].

More recently, patients with inherited disorders of the IL-12–IFN-γ axis [15, 16] were shown to be vulnerable to poorly virulent mycobacteria, such as bacille Calmette-Guérin (BCG) vaccine and environmental nontuberculous mycobacteria (NTM), as well as to nontyphoid Salmonella species. The vulnerability to Salmonella species is a well-known feature of the syndrome of mendelian susceptibility to mycobacterial disease: approximately one-half of patients with this syndrome have salmonellosis [17, 18]. Patients may bear mutations in IFNGRI, IFNGR2, and STAT1, impairing the cellular responses to IFN-γ, or in IL12B and IL12RB1, impairing the production of IFN-γ. Salmonellosis has been associated with each of these genetic defects, with the exception of STAT1 deficiency. Different Salmonella serotypes (mostly S. Enteritidis and S. Typhimurium) have been implicated. Salmonellosis was particularly frequent among children with IL-12 receptor β1 (IL-12Rβ1) deficiency; however, in all cases, it was associated with mycobacterial infection.

We describe what is, to our knowledge, the first child who presented with isolated, recurrent, mostly asymptomatic cases of Salmonella bacteremia due to IL-12Rβ1 deficiency.

Case report. A 12-month-old Bedouin Arab boy, who had been born in a normal delivery after an uneventful pregnancy, was admitted to the hospital because of irritability, swelling of
both legs, and leg pain. The child had been born to young and healthy parents who are first cousins. His 3 siblings are healthy. He received all of his scheduled vaccinations on time, without apparent unwanted effect. However, he had not been vaccinated with BCG.

At hospital admission, the patient was in good general condition. His body temperature was 37.1°C. Physical examination revealed mildly enlarged axillary and inguinal lymph nodes and a hemorrhagic-vasculitic rash on both legs. A complete blood cell count revealed a WBC count of 18,700 cells/mm³ (39% polymorphonuclear cells and 6% bands) and a platelet count of 545,000 platelets/mm³. The erythrocyte sedimentation rate was 130 mm/first hour, and chemistry analysis revealed an alanine aminotransferase level of 169 IU/L and an aspartate aminotransferase level of 69 IU/L. A blood culture grew ceftriaxone-susceptible group D Salmonella species, and the patient was treated with ceftriaxone for 15 days.

One week after completion of treatment, a follow-up examination revealed that the child was asymptomatic and had an elevated erythrocyte sedimentation rate. A blood culture was positive for group D Salmonella species, and the isolate had an antibiotic susceptibility profile identical to that of the previously yielded isolate. Homogenous hepatomegaly, without evidence of ascites or enlarged lymph nodes, was evident on abdominal sonography. The patient was treated with ceftriaxone for another 15 days. During this therapy, blood cultures were sterile.

Two weeks after the conclusion of treatment, the patient was admitted to the hospital again because of group D Salmonella bacteremia. This time, his work-up revealed hepatosplenomegaly and a massive pericardial effusion. The results of serological tests for Epstein-Barr virus, cytomegalovirus, HIV, and Schistosoma species were negative. Analysis of a fecal sample failed to reveal parasites. Pericardiocentesis was performed, and treatment with intravenous ceftriaxone was administered for 21 days. The results of blood cultures were negative at the end of treatment. Analysis of pericardial effusion was consistent with a sterile reactive fluid.

During the next 18 months, the patient had 6 more episodes of asymptomatic Salmonella bacteremia caused by the same serovar that had previously been recovered. The patient was examined at routine follow-up visits; on every occasion, he had no physical complaints, and no abnormalities were found during physical examination. Each time, group D Salmonella species grew on culture of his blood, and he was treated with ceftriaxone on each occasion except for the last one, when ciprofloxacin was administered for 6 weeks. Six of 8 group D Salmonella isolates were available for molecular typing by PFGE (figure 1) [19]. All isolates had identical DNA fingerprints, indicating that all 6 episodes of bacteremia originated from the same serovar.

The patient had 1 episode of benign Kingella kingae bacteremia at the age of 3 months. At the age of 4 months, he was admitted to the hospital because of epididimitis and high fever, and his blood culture was positive for Streptococcus pneumoniae serotype 9a. In both cases, he responded well to a single course of antibiotic treatment.

Immunologic studies performed when the patient was asymptomatic revealed a normal complete blood cell count, normal immunoglobulin level, normal levels of complement components C3 and C4, and normal proportions of lymphocyte subpopulations, such as CD2, CD3, CD4, CD8, CD16, CD19, CD20, CD45, and CD56 cells. The result of a PPD skin test was negative. There was a normal response of lymphocytes to mitogens, such as phytohemagglutinin (PHA) and concanavalin A, and to Candida antigen. Neutrophil functions, including chemotaxis, phagocytosis, and superoxide generation, were within normal ranges. When the patient’s blood cells were stimulated with live BCG and IL-12, the amount of IFN-γ secreted in the supernatant was not elevated, compared with BCG stimulation alone, indicating that there was an impaired cellular response to IL-12. The IL-12Rβ1 expression on PHA-driven blasts...
was diminished when examined by fluorescence-activated cell-sorter (FACS) analysis that used 2 different monoclonal antibodies [20]. An in-frame large deletion encompassing exons 8–13 in the IL12RB1 gene, which encodes the IL-12Rβ1 chain, was found. The parents were heterozygous for this deletion, and the healthy siblings were either homozygous for the wild-type allele or heterozygous for the mutant allele. Because a residual IL-12Rβ1 expression was revealed on the patient’s PHA blasts cell surface, we stimulated them with increasing doses of recombinant human IL-12, to verify that the mutant allele, if expressed, was nonfunctional. PHA blasts either were not stimulated or were stimulated with recombinant human IL-12 in the patient, in a known IL-12Rβ1−deficient patient (patient 2 in [21]), in a healthy control subject, and in the patient’s mother. IFN-γ was not detected in the supernatants of our patient’s cells or in those of the IL-12Rβ1−deficient patient’s cells, whereby comparable amounts of IFN-γ were detected in the supernatants of the healthy control subject’s cells and the patient’s mother’s cells (figure 2). These data established unambiguously that the child had a complete IL-12Rβ1 deficiency.

Discussion. We present what is, to our knowledge, the first case of an IL-12Rβ1−deficient patient with recurrent episodes of group D Salmonella bacteremia during a period of 18 months, despite repeated courses of antibiotic treatment.

Mutations in the IL12RB1 gene encoding the β1 chain of the IL-12 receptor have been described in several families [22–28]. These mutations were missense, nonsense, and splice mutations, all leading to lack of receptor expression on the cell surface and abolished cellular responses to IL-12 [15]. Complete IL-12Rβ1 deficiency is associated with a selective susceptibility to severe infections caused by poorly pathogenic mycobacteria, such as BCG vaccines and environmental NTM [16]. Some of the patients had an increased susceptibility to Salmonella infection that appeared separately or concomitantly with the mycobacterial infection; in one case, this occurred before the onset of mycobacteriosis [22, 23]. Our patient had recurrent Salmonella bacteremia events and isolated infections with Kingella and S. pneumoniae but no evidence of mycobacterial infection. Appropriate treatment of the Kingella and pneumococcal infections resulted in prompt recovery, whereas the Salmonella infections recurred, with episodes of bacteremia over 18 months caused by an identical bacterium, despite repeated courses of antibiotics, which indicates that this patient may have a problem clearing intracellular rather than extracellular bacteria.

Bacteremia due to both Kingella and S. pneumoniae serotype 9a are quite common in southern Israel, especially among young Bedouin children [29, 30]. The patient had not been immunized against either Kingella species or S. pneumoniae; however, he mounted an adequate antibody titer to both infections. None of the 50 patients with IL-12Rβ1 deficiency known to us experienced pneumococcal infection, despite exposure to pneumococci. It is possible that the Kingella infection could have been fortuitous or related to IL-12Rβ1 deficiency, because, unlike pneumococcus, this germ is more limited geographically. The absence of mycobacterial disease may be due to a lack of exposure, because the child had not been vaccinated with BCG, and there is no evidence that he was infected with NTM, as suggested by a negative PPD skin test result.

True resistance to mycobacterial infection is an alternative hypothesis, which is supported by our recent observation that the penetrance of IL-12Rβ1 deficiency is surprisingly low [20]. Only one-half of IL-12Rβ1−deficient children who are not vaccinated with BCG develop clinical disease due to NTM, generally before the age of 10 years. One patient with IL-12Rβ1 deficiency, who was described elsewhere [23], had been vaccinated with BCG without adverse effects, had Salmonella lymphadenitis at the age of 12 years, and had environmental mycobacterial infection at the age of 17 years. A careful follow-up of our patient until at least the teenage years is required to assess whether he is vulnerable or resistant to NTM. He may even develop tuberculosis, as occurred in 2 siblings (I. Caragol et al., personal communication) [26].

In any case, this is the first report of a patient with IL-12Rβ1 deficiency who presented with isolated salmonellosis. A single patient with IL-12B deficiency who had only Salmonella infection without any mycobacterial involvement was described else-

![Figure 2. Impaired cellular response to IL-12. Diluted whole-blood samples obtained from a healthy local control subject (C+), the case patient (P), and a known IL-12 receptor β1−deficient patient (C−) either were not stimulated (−/−) or were stimulated with bacille Calmette-Guérin (BCG) alone (−/+), or BCG plus recombinant IL-12p70 (20 ng/ml; +/+). Samples of fresh, heparinized blood obtained from the patient and the “travel” control subject were shipped to Paris within 48 h, where the experiment was performed. The supernatants were harvested after 48 h of activation for IFN-γ quantification by ELISA.](image-url)
where [21]. This patient carried a mutation in the IL-12B chain gene, unlike our patient, who had a mutation in the cytokine’s receptor gene. In conclusion, diagnosis of IL-12Rβ1 deficiency should be contemplated for children with recurrent salmonellosis, even in the absence of any personal or familial history of mycobacterial infection.

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References


