

A Novel Homozygous Mutation With Different Clinical Presentations in 2 IRAK-4-Deficient Siblings: First Case With Recurrent Salmonellosis and Non-Hodgkin Lymphoma

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Interleukin-1 receptor-associated kinase-4 (IRAK-4) deficiency (OMIM 607676) is an autosomal recessive disorder. Patients with IRAK-4 deficiency have been prone to systemic and peripheral pyogenic bacterial diseases [1]. More than 50 IRAK-4-deficient patients have been reported worldwide [2]. Here, we report a novel homozygous *IRAK4* gene mutation in 2 siblings who presented with distinct features.

Patient 1 was a 4-month-old girl born to consanguineous parents admitted with vomiting and tonic-clonic seizures. She was diagnosed with *Pseudomonas aeruginosa* meningitis. She had a history of delayed umbilical cord separation (30 days). Laboratory evaluation revealed a high erythrocyte sedimentation rate (ESR) (123 mm/h) and C-reactive protein (CRP) (169 mg/L). The IL-6 response after stimulation with lipopolysaccharide or IL-1 β was defective. Sanger sequencing of the *IRAK4* gene revealed a novel

homozygous missense loss-of-function mutation in exon 3 of *IRAK4* (c.161G>A, p.R54K, at protein level). The patient is now 18 months old and has epilepsy and mental-motor retardation, although she has not experienced severe infection since she started intravenous immunoglobulin G replacement treatment.

Patient 2 was the brother of patient 1 (age 14 years). He was diagnosed after family screening and found to have the same homozygous mutation. He had a normal interval for umbilical cord separation (10 days), oral moniliasis since age 3 months, recurrent skin abscesses since age 9 months, recurrent bronchopneumonia since age 1 year, and an abdominal mass due to gastric lymphoma with metastasis on the liver at 26 months. Laboratory evaluation revealed high IgE (1084 IU/mL), IgG (1830 mg/dL), ESR (66 mm/h), and CRP (150 mg/L). *Staphylococcus aureus* was detected in a culture of intraabdominal fluid. Analysis of a biopsy specimen revealed grade 3 T-cell non-Hodgkin lymphoma (NHL). *Enterococcus faecalis* was detected in urine culture, group C1 *Salmonella* in stool culture (4 times), *Staphylococcus hominis* in blood culture, and *Candida albicans* in throat culture. Appropriate antibiotics and chemotherapy were started. Two months after the diagnosis of NHL, a septated abscess (4×4×6 cm) was detected between the stomach and the liver. The patient had recurrent convulsions and experienced difficulty walking at age 29 months. Cerebrospinal fluid culture yielded no microorganisms, although group C1 *Salmonella* was isolated from blood culture. During treatment with ciprofloxacin, group C1 *Salmonella* was again detected in stool culture. Values for *Salmonella* agglutinins were high. Multiple abscesses were found to persist in the liver until age 35 months. The last chemotherapy was administered at 42 months of age. The patient was diagnosed with epilepsy at age 10 and started antiepileptic treatment for 3 years. He is now 15 years old and has learning difficulties and behavioral problems. He still has mild recurrent skin abscesses that resolve with local/oral antibiotics. The Figure shows a skin abscess on his knee.

Toll-like receptors and interleukin-1 receptors play a role in the recognition of microbial components and signal via myeloid differentiation primary response 88 (MyD88) and IRAK-4. Patients with MyD88 and IRAK-4 deficiency are



Figure. Skin abscess in Patient 2.

highly susceptible to invasive pyogenic diseases caused by *Staphylococcus pneumoniae*, *S aureus*, and *P aeruginosa*. However, clinical and laboratory signs of inflammation develop slowly, even in cases of severe infection, and they may be difficult to diagnose [2]. Although the patients we report had invasive pyogenic infections, they did not have leukocytosis on admission. *Salmonella* infections have not been reported in patients with IRAK-4 deficiency to date, although they have been reported in patients with MyD88 deficiency, mendelian susceptibility to mycobacterial disease (MSMD), and chronic granulomatous disease (CGD) [2]. To our knowledge, this is the first report of recurrent *Salmonella* infection in a patient with IRAK-4 deficiency.

Besides IRAK-4 and MyD88 deficiency, severe congenital neutropenia, cyclic neutropenia, specific granule deficiency, CGD, hyper-IgE syndrome, leukocyte adhesion deficiency (LAD), MSMD, and Wiskott-Aldrich syndrome should be kept in mind in patients with recurrent skin and/or deep organ abscesses [3,4]. Most of these disorders were excluded by laboratory evaluation in the patients reported here.

Notably, two-thirds of reported IRAK-4- and MyD88-deficient patients were found to have high levels of IgE, although these levels were modest with respect to the very high IgE levels described in STAT-3-deficient patients. Patient 2 also had high IgE levels at 2 years of age, when he was hospitalized for NHL and suspected liver abscess, which normalized at age 14 years (55 IU/mL).

Umbilical cord separation requires MyD88- and IRAK-4-dependent signals, as well as CD18-expressing leukocytes. Some primary immunodeficiencies, such as LAD type1 and Rac2 deficiency, have been associated with delayed separation of the umbilical cord and/or omphalitis, extremely high levels of circulating neutrophils, and a lack of pus formation in peripheral tissues [5]. By contrast, in IRAK-4- and MyD88-deficient patients, impaired polymorphonuclear neutrophil mobilization and pus formation occur during infections, perhaps secondary to the lack of IL-8 production [2].

Primary immunodeficiencies are also associated with an increased risk of malignancy. Some reports based on MyD88-deficient (*Myd88*^{-/-}) mice showed a protective role of MyD88 in carcinogenesis [6]. This can be explained by increased epithelial apoptosis and proliferation in MyD88-deficient mice. Malignancy has not been reported to date in humans and mice with IRAK-4 deficiency.

The prognosis of IRAK-4 deficiency is poor in early childhood, with a mortality rate of 38%, although it improves substantially in adolescence. No deaths were recorded in patients after the age of 8 years, and no invasive infection after the age of 14 years. Improvement in symptoms with age may result from the reconstitution of adaptive antigen-specific T- and B-lymphocyte responses [2]. This finding is probably unique in the field of primary immunodeficiencies, which do not improve with age. A similar but less striking spontaneous improvement has only been reported in children with IL-12p40 and IL-12Rβ1 deficiencies [7]. Consistent with this observation, the frequency and severity of infections improved over time in Patient 2.

In conclusion, IRAK-4 deficiency should be considered in patients with invasive infection by *Pseudomonas*, *Staphylococcus*, and even *Salmonella* species. It is important

to initiate empiric parenteral antibiotic treatment as soon as infection is suspected without taking inflammatory parameters into account, because patients may die from rapid invasive bacterial infection, even if prophylactic measures are taken. Patient 2 is the first reported case of IRAK-4 deficiency with recurrent salmonellosis and malignancy.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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