ESPID -0289

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Primary Deficiency of Interleukin-1 Receptor-Associated Kinase (IRAK-4) Presenting as Fatal *Pseudomonas aeruginosa* Bacteremia in Two Siblings

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Abstract

Background and aims: *Pseudomonas aeruginosa*, a Gram-negative bacillus and an opportunistic ubiquitous environmental microorganism, causes serious infection in children with immunodeficiencies. Deficiency of interleukin-1 receptor-associated kinase (IRAK-4), which is a protein of the Toll–IL-1R (TIR) intracellular signal transduction pathway, confers a predisposition to invasive bacterial infection. We present a case of fulminant *P. aeruginosa* sepsis in a child with previously undiagnosed IRAK-4 immunodeficiency, whose sibling presented one year earlier with a similarly fatal event.
Methods: A previously healthy 14-month old boy presented with sepsis and died within 48 hrs in the emergency department from disseminated *P. aeruginosa* infection. Fibroblasts from the deceased child were cultured and used for DNA extraction. PCR was performed and its products were sequenced for detecting IRAK-4 mutations. A functional assay was performed on fibroblast cells from the patient, healthy control, and IRAK-4 deficient patient upon stimulation with IL-1b.
Results: The child was found to be compound heterozygous for mutations in both alleles of the gene encoding IRAK-4. A splice mutation 1189-1G >A was transmitted by the mother and a splice mutation 831+5G >T was transmitted by the father. The parents had no medical history of immunodeficiency. The functional study on fibroblast cells found an absence IL-6 production upon IL-1b stimulation that confirmed the impairment of TIR signaling pathway in the patient's cells. The sibling was also inferred to have familial IRAK-4 deficiency.
Conclusions: Fulminant *P. aeruginosa* sepsis in early childhood may present as the primary manifestation of IRAK-4 deficiency.

Background-Objective

Pseudomonas aeruginosa, a Gram-negative bacillus and an opportunistic environmental microorganism, causes serious infections in children with impaired defence mechanisms and chronic diseases. *Pseudomonas* sepsis is rare in healthy children and the empirical antibiotic treatment for sepsis does not include agents against this microorganism. Among the primary immunodeficiencies (PIDs) which predispose to *P. aeruginosa* sepsis are the impairments of Toll-like receptor (TLR) –interkeukin-1R (IL-1R) intracellular signal transduction pathway proteins, such as the interleukin (IL)-1 receptor-associated kinase 4 (IRAK-4) and myeloid differentiation factor (MyD)88. Leukocytes from these patients do not respond to stimulation with cytokines of the IL-1 superfamily such as IL-1β or IL-18, as well as stimulation with agonists of the Toll-like receptors, except with TLR3 agonist. Due to this impaired activation of innate immune responses, IRAK-4-deficient patients develop recurrent pyogenic bacterial infections, while retaining a normal resistance to common fungi, parasites, and viruses. Herein, we report a case of two siblings with fatal fulminant *P. aeruginosa* sepsis as initial presenting manifestation of IRAK-4 deficiency

Case Report

Present Medical History: A previously healthy 14 month old male was admitted to the emergency department of the University Hospital of Liege with:

• a history of two days fever up to 39.9°C
• upper respiratory symptoms
• and fatigue.

Past Medical History:
• no sick contacts
• no history of repeated infections or recent travel and n
• no known drug allergies
• immunizations appropriate for age.
•the separation of umbilical cord in both children took place three to four weeks after the birth.

Family Medical History:
• no contributory medical history from his parents. The father and the mother had Belgian and Russian origin, respectively, and they lived in Belgium.
• his sister died at the age of 18 months due to fulminant *P. aeruginosa* septic shock.

Physical Examination:
• weakness, nasal secretions, and tachypnea
• temperature was 39.9°C, pulse 163/min, and O2 saturation 100%
• ecthyma gangrenosum

Case Report

Laboratory Studies:
• WBC: 5260/mm3 (47.3% neutrophils, 35.5% lymphocytes), hemoglobin: 12.2 g/dl, platelet count 250,000/mm3 and CRP: 8.8 mg/L.
• Urine analysis was normal
• Cultures of blood and cerebrospinal fluid grew *P. aeruginosa*, which was pan-susceptible.

Progress:
• Five hours after admission, the child developed respiratory distress and diffuse petechiae.
• Distributive shock was diagnosed and the appropriate resuscitation protocol was started.
• Despite the resuscitation efforts with intubation and inotropic support, the child died.

Functional studies and genetical ananlysis after the child's death:
•. A functional assay was performed on fibroblast cells from the patient, one control patient and IRAK-4-deficient patient upon stimulation with IL-1β or tumor necrosis factor alpha (TNF-α).
• The functional study on the patient´s fibroblasts cells and on those from the IRAK-4-deficient patient found an absence IL-6 production upon IL-1β stimulation that confirmed the impairment of TLR–IL-1R signalling pathway (figure 1).
• The fibroblasts were cultured for DNA extraction and PCR was performed. The child was found to bear compound heterozygous splice mutations in the IRAK4 gene. The mother was found to be heterozygous for the splice mutation 1189-1G>A and the father heterozygous for the splice mutation 831+5G >T.

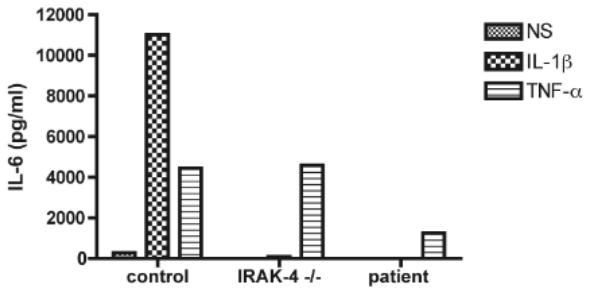

Figure 1. Interleukin-6 (IL-6) production after stimulation during 24 hours with interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α) by fibroblasts of healthy control, IRAK-4 -/- deficient patient, and the index patient reported herein.
NS: non stimulated

Conclusions

✓ IRAK-4 deficiency should be considered as a part of the differential diagnosis of fulminant *Pseudomonas* sepsis in children and appropriate genetic investigation should be initiated

✓ IRAK-4 deficiency can be considered among other primary immunodeficiencies if delayed umbilical cord separation is observed

✓ The splice mutation 1189-1G>A, responsible for IRAK-4 deficiency, is demonstrated for the first time

✓ IRAK -4 deficiency can be detected in different national backgrounds

References: 1 Picard , et al., Medicine 2010; 89:403-25.
2. Cardenes M, et al. The Journal of pediatrics, 2006; 148:549-51.