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IRAK 4 Deficiency Associated With Group B Streptococcus and Pseudomonas Aeruginosa Infection: A Case Report

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Abstract: **Interleukin receptor associated kinase (IRAK)- 4 deficiency is a rare disorder of primary innate immunity. Anecdotal evidence has existed for more than a decade and although major pathogens are bacteria, rare instances of infection with fungi and opportunistic organisms have also been reported. We report a case of a female infant presenting with recurrent bacterial infections with Group B streptococci and Pseudomonas aeruginosa secondary to IRAK-4 deficiency.**

Keywords: **IRAK-4 deficiency, Pseudomonas aeruginosa, Group B streptococcus, infant.**

1. INTRODUCTION

Human Interleukin 1 receptor associated kinase d (IRAK-4) deficiency is a rare disorder of primary innate immunity (1). The first case was reported in 2003(2). It is identified by the Online Mendelian Inheritance in Man (OMIM) identifier #607676 (1). Few cases have been reported from 4 continents i.e. Americas, Asia, Australia and Europe describing the clinical manifestations and laboratory findings suggestive of the disorder (1, 3-6).

This autosomal recessive disorder impairs Toll-like receptor (TLR) and interleukin-1 receptor mediated immunity (3). IRAK 4 plays an important role in signal transduction involving IL-1, IL-18 and TLRs except TLR 3(1). The cases may be found clustered within families although non-consanguinity of parents does not rule out the possibility of inheritance (1).

Here we present an interesting case of a baby girl presenting with IRAK-4 deficiency.

2. CASE SUMMARY

We report the rare case of a one year old full term girl born through a spontaneous vaginal delivery carrying a birth weight of 3.8 kg resident of Riyadh.

The baby was in her usual state of health till one month of age when she developed gastroenteritis treated with anti-parasitic drugs at a local clinic with partial improvement according to history. At the age of 3 months the patient was treated for Streptococcus agalactaie (GBS) bacteremia complicated by osteomyelitis and sub periosteal abscess of the right shoulder and left femur. She was treated with penicillin G for a period of 3 weeks which led to complete resolution of infection. Unfortunately, when she was 6 months old she developed Pseudomonas bacteremia complicated by an appendicular mass. She underwent drainage and received intravenous antibiotics for 14 days. But even after receiving antibiotics she developed an abscess on her abdominal wall at the site of the drain. Percutaneous abscess drainage (PAD) was carried out and intravenous antibiotics were continued for a total of 4 weeks which led to resolution of her infection.

Her parents had a consanguineous marriage and she had 2 older siblings who were healthy and alive. There was history of neonatal death in 2 of her cousins due to infections. There was history of Propionic academia in her maternal family. She received birth vaccines and had an unremarkable developmental history.

During physical examination at age of 1 year she was well looking playful pleasant child active and interactive with her parents, had stable vital signs and average growth parameters. Her abdomen was soft and lax with 2 small surgical scars 1*1 cm in the right lower quadrant with no tenderness, organomegaly or masses .Chest and cardiovascular examination were unremarkable. Joints were normal with no swelling or tenderness; there was no lymphadenopathy, pallor or jaundice.

Blood workup during the first episode of illness with osteomyelitis showed hemoglobin was 10.5 g/dL with MCV 68.8 fL. White blood cell count was 8.3 X 10^9/L comprising of 68% neutrophils and 22% lymphocytes. Platelet count was 371 X 10^9/L. Her ESR was 43 mm/hour and CRP was 18.9 mg/L. Culture results have been mentioned above with the respective episodes of infection.

Absolute CD3 count was 4.4 X 10^9/L (84.3%), absolute CD4 count was 3.6 X 10^9/L (69.3%), absolute CD8 count was 0.8 X 10^9/L (14.6%) and the absolute CD19 count was 0.5 X 10^9/L (10.2%). Flow cytometry showed CD4/CD8 ratio 4.7 with T lymphocytosis and B lymphopenia. Intact expression of MHC class II antigens on B lymphocytes was observed. Activated T cells (CD3+DR+) were 1.5%. CD 16-56% was 4.4%.

Immunoglobulin G was 14.7 g/L (Ref: 1.8-6.0 g/L) while IgA and IgM were 0.7 g/L and 1.1 g/L (within the reference range).

Since the age of 6 months the patient was maintained on monthly IVIG and is thriving well. Currently she is on regular fellow up at pediatric immunology clinic.

3. DISCUSSION

IRAK-4 deficiency has been reported from Saudi Arabia before (4). An interesting finding in IRAK-4 deficient patients has been the delayed separation of umbilical cord reported even later than 21 days in half of the patients in one case series from Japan (1). Interestingly, the same authors reported no abnormality in serum Immunoglobulin levels, natural killer cell subsets and lymphocyte subsets in their patients (1). Also the peripheral white blood cell count and C-reactive protein levels were normal in the series of 10 patients reported from japan (1). In our patient the white blood cells and serum IgM and IgA were found to be normal while IgG was elevated which is in contrast to a study by Maglione et al who report that abnormalities are found in Immunoglobulin M and not G in patients with IRAK-4 deficiency expressing as a reduced expression and defective function of IgM (5)

Despite affecting a wide range of immunological processes the observed clinical manifestations suggest a narrow range of susceptibility to bacterial pathogens leading to pyogenic bacterial infections like meningitis, osteomyelitis, sepsis, arthritis and abscesses (2, 4, 7-9). Other presentations include skin infections, ENT infections, lymphadenitis, intracranial abscess and pneumonia (4, 10). Pneumococcal Meningitis was identified as the most common cause of death in the Japanese study (1). The fulminant nature of infection within the first 24 hours leads to death (1).

Isolated reports can be found presenting as pericarditis, liver and paratracheal abscesses (11). One case of Non-TB mycobacterial abdominal abscess with intestinal perforation has also been reported in literature (12). One of the earliest reported cases was complicated by a course of repeated infections by gram positive, gram negative bacteria, fungi and opportunistic organisms in an 8 year old girl (13). It is interesting to note that a case of an adult woman with homozygous IRAK-4 deficiency was misdiagnosed as Hyper IgE (Immunoglobulin E) syndrome presenting with repeated skin infections and lung abscesses (14).

The most commonly isolated pathogens are Streptococcus pneumonia in more than 50% of the cases, Staph aureus in 14% and Pseudomonas aeruginosa in 19%(4, 15-17).Our patient also had invasive infection with Pseudomonas aeruginosa .Other rare pathogens reported till date include 2 cases of Shigellosis and 2 cases of Group B streptococcus infection similar to our patient (4, 18).

Authors in the Japanese study identified a screening method by TNF-alpha producing monocytes after in-vitro Lipopoly saccharide stimulation were deficient in all patients alive in their case series (1).

Management involves early identification from patient's and family's history, immunization against Streptococcus pneumonia, Nisseria meningitides and Hemophilus influenzae. A prophylactic antibiotic regimen of Cotrimoxazole and Penicillin V for life is suggested to improve the long term outcome of these patients. If the deficiency is severe, regular Immunoglobulins (IgG) are recommended till the age of 10 years (4). It is observed that after this age, the patient's immunity is enough to sustain the virulence of pathogenic bacteria and leads to a conclusion that probably IRAK-4 is redundant for adult immunity (19) . Although there has been a case reported where despite 2 years of prophylaxis with IVIG, the patient develops life- threatening meningitis (20). We managed the patient in accordance with the existing evidence and the patient is under follow-up.

4. CONCLUSION

We report a case of IRAK-4 deficiency diagnosed by clinical presentation of repeated bacterial infections currently stable and managed with IVIG.

Ethical approval:

The patient's parents provided assent for the publication of this report.

Conflict of interest:

The authors declare that there are no conflicts of interest.

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