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PAEDIATRICS
Case Report

Hyper Immunoglobulinemia D syndrome in a Saudi girl: A Case Report

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Abstract

An eight years Saudi girl from consanguineous parents died after long history of mysterious febrile disease diagnosed and treated as Familial Mediterranean fever. Genetic studies showed double homozygous mutation V377I which is characteristic of hyper immunoglobulin-D syndrome (HIDS). This is the first reported case of hyper immunoglobulin-D from Saudi kingdom.

Keywords: *Hyperimmunoglobulinemia D syndrome; Periodic fever; Saudi girl*

Abbreviations: HIDS: Hyperimmunoglobulinemia D Syndrome; MK: Mevalonate Kinase; CRP: C Reactive Protein; KSA: Kingdom of Saudi Arabia; FMF: Familial Mediterranean fever

Introduction

Hyper Immunoglobulinemia-D syndrome (HIDS) was first described in 1984 by Van Deer Mer in patients with periodic fever and Dutch ancestry and named auto inflammatory disease not autoimmune diseases because of the absence of antibodies [1,2].

HIDS is a rare autosomal recessive disease. It is caused by an inborn error of cholesterol biosynthesis brought about by a gene mutation (MVK), controlling an enzyme called mevalonate kinase (MK) located on chromosome 12q24 [3]. More than 60 mutations have been reported but more frequent are V377I and I268T [4]. These mutations causes variable degrees of deficiency of mevalonate kinase (MK) which will lead to a defects in the production of isopronoids and steroids resulting in bouts of inflammation that involve many organs mainly gastrointestinal, musculoskeletal and the skin. clinical features include severe diarrhoea, arthralgia, rash and mouth ulcers and Laboratory features include an acute phase response (elevated CRP and ESR) and markedly elevated IgD (and often IgA), although cases with normal IgD have been described. Most cases are reported in the Northern countries in the west are perhaps causes by founder effect. Herein, we report a second HIDS case in a female Saudi girl from the Arab world.

Case Report

An 8 year-old Saudi girl has been frequently admitted to hospital since the age of 1 year because of recurrent attacks of fever that lasted for about one week. The attacks were preceded by malaise, rigors and chills which were accompanied by gastrointestinal manifestations mainly vomiting, abdominal pain and watery diarrhea leading to severe dehydration. Over the years she developed also symmetrical arthritis of the large joints. By the age of six years, she started to use a wheelchair during her attacks due to her severe knees arthritis. She had a generalized maculopapular rash, acute myositis, vertigo and severe headache, ataxia and febrile seizures.

She had many hospital admissions during the year between 2006 and 2012, during her attacks she was miserable and became very sick. Antibiotics were prescribed each time because of high fever, CRP and ESR but were ineffective most of the times. In the last two years other therapies as colchicine, corticotherapy and parenteral hydration were given, and were more effective.

She often needed blood transfusions for severe microcytic hypochromic anemia which didn't respond to iron therapy. Laboratory findings showed an acute phase response of leucocytosis of 30000, C reactive protein 400 and ESR 120. Complete recovery and normalization of these critical values between attacks took 4 to 12 weeks. Renal, hepatic and cardiovascular examinations were completely normal.

Infectious causes as primary immunodeficiency, autoimmune diseases and neoplastic syndromes have been checked for and were excluded during the course of the disease over the years. Immunoglobulin subclass IgG 4 was found to be low in one occasion. This finding couldn't explain the symptomalogy of this child. The rest if IgG subclass were in the normal range measured many times, IgA, IgM, IgE levels were normal and IgD level was not measured.

Imaging studies showed a splenomegaly with swollen mesenteric lymph nodes during attacks whereas the bone marrow aspiration and biopsy, electroencephalogram EEGs and the brain imaging were all normal. Upper and lower endoscopies with biopsies were all normal also.

By the age of 6 year colchicines therapy was given and her attacks became less frequent and less severe, but this medication was discontinued when genetic studies for Familial Mediterranean fever were negative. However this therapy was resumed due to its beneficial effects on the child's health. A short course of intravenous corticotherapy during the attacks was very successful and the fever resolved in less than 48 hours (1 mg/kg/day of methylprednisolone for five days). Sometimes prednisolone syrup at 1 mg/kg/day was given for duration of one week when fever and vomiting began which ameliorate the patient and avoided the patient admission to hospital.

After the age of eight years she had her last febrile attack was complicated by severe status epilepticous and multi-organ failure which leads to her death [5]. Finally an Extensive genomic study on periodic fever was done in a highly specialized laboratory showed a homozygous mutation V377I. Blood samples were sent to the national human genome research institute to look for possible mutations that could explain the disease other than FMF mutations because genetic studies for FMF were negative. Unfortunately the results came soon after patient death.

Discussion

This is the first case of HIDS from kingdom Saudi Arabia (KSA), and second reported case from Arab world, First case was reported by doctor Hammoudah from Palestine in 2004 [6]. A recent review of 50 patients from Europe show that many cases of HIDS occur in people of Arabic ethnicity [7]. The rarity of this disease was due to delay in diagnosis, since most cases of periodic fever were considered to be Familial Mediterranean Fever (FMF) which are prevalent and known in KSA [8]. The clinical presentation of our patient was similar to that described in the literature by the irregularity of fever attacks [9]. There was no evidence that the onset of attacks was related to a vaccine, trauma or stress [10]. A sub group of HIDS patients can develop neurological manifestations of variable degrees such mental retardation, ataxia and ocular symptoms.

These findings can be related to a continuum spectrum between the mevalonic aciduria (severe form of mevalonate kinase deficiency) and HIDS (partial form of mevalonate kinase deficiency) [11]. Our patient had febrile convulsions. She had also severe vertigo which leads to inability to stand or walk during attacks. Our patient had normal immune profile except for low IgG 4 and this was reported by one study [12]. The treatment of HIDS patients using colchicines is controversial; most data showed no benefits although a few cases did show improvement as occurred for in our patient [13]. There are other treatments as etanercep, TNF-alpha inhibitor, anakinra, IL-1 receptor antagonist but none were tried in our patient. Similar results have been found for intravenous corticoid given for short periods during the attacks [14]. The genetic studies show that a V377I mutation is present almost in 80% of HIDS cases [15].

Conclusion

The diagnosis of hyper IgD syndrome for the first time in Saudi Kingdom should raise the awareness of the importance of genetic study in any patient with periodic fever. More of research is needed for treatment of HIDS to avoid severe morbidity and mortality related to this disease.

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