Novel Mutations causing Hyperimmunoglobulin D and Periodic Fever Syndrome

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Hyperimmunoglobulin D and periodic fever syndrome (HIDS) is a rare, hereditary autoinflammatory condition characterized by recurrent inflammatory episodes. We report a 9-year-old boy, diagnosed with HIDS due to two novel mutations, c.62C>T (p.Ala21Val) and c.372-6T>C (probable splicing defect), in the *mevalonate kinase* (*MVK*) gene. The pathogenicity of these mutations was confirmed by measurement of low MVK enzyme activity in cultured primary skin fibroblasts of the patient. The symptoms have been refractory to therapy with steroids and non steroidal anti inflammatory drugs. This report expands the genetic and ethnic spectrum of HIDS.

Key words: *Diagnosis, HIDS, India, Mevalonate kinase, Mutation.*

Hereditary periodic fevers are rare, autosomal recessive diseases characterized by apparently spontaneous attacks of inflammation [1]. Hyper IgD syndrome (HIDS, OMIM #260920) is one such entity caused by mutations in the gene encoding mevalonate kinase (MVK), an enzyme involved in the isoprenoid and cholesterol biosynthesis pathway [1]. We report its sporadic occurrence in an Indian boy in whom two novel *MVK* gene mutations were identified.

CASE REPORT

A 9-year-old boy born to non-consanguineous parents was admitted with fever, abdominal pain, poor intake, oral ulcers, cervical lymphadenopathy, loose stools and skin rash. Recurrent attacks of high fever were reported since infancy. During each attack, high grade fever, anorexia, loose stools with mucus and/ or blood, and tender lymphadenopathy of the neck, axillae and groins were present. Inconsistently, findings included abdominal pain, oral ulcers, blanching maculopapular rash, arthralgias or arthritis involving large joints, and eye congestion. Symptoms would resolve in 15-20 days, and then recur following an asymptomatic interval of 20 days to several months. There was no history of malar rash, photosensitivity, Raynaud's phenomenon, morning stiffness or muscle weakness, and no family history of similar complaints. On admission, the child was cachexic and febrile. Examination revealed maculopapular rash all over the body, with generalized tender lymphadenopathy, aphthous oral ulcers, hepatosplenomegaly (3 cm each), and bilateral few rhonchi. There was no uveitis or arthritis.

Differential diagnoses included immunodeficiency, juvenile rheumatoid arthritis, periodic fever, and connective tissue disorder. Therapy with intravenous antibiotics and paracetamol was started, and one dose of intravenous hydrocortisone administered for wheezing. Hepatosplenomegaly, rash, rhonchi and lymphadenopathy resolved in 48 hours. By day 7 all symptoms and signs had disappeared.

At admission, investigations showed neutrophilic leukocytosis (total count 20,400/mm^3, 64% neutrophils), normocytic normochromic anemia, normal renal and liver function tests, and elevated erythrocyte sedimentation rate and C reactive protein. Blood and urine cultures were sterile, chest radiograph showed clear lung fields, while stool and urine examination were unremarkable. Immunological testing showed normal C3 complement, absence of rheumatoid factor, antinuclear, anti-dsDNA and anti neutrophilic cytoplasmic antibodies, negative HIV serology and normal nitroblue tetrazolium test. Serum IgG (1105 mg/dL, range 600-1236 mg/dL) and IgM (159 mg/dL, range 99-196 mg/dL) levels were normal, while IgA was increased (417 mg/dL; range 25-154 mg/dL). Fine needle aspiration and biopsy of cervical lymph node suggested reactive hyperplasia. Lipid profile was unremarkable except for an elevated triglyceride level of 840 mg/dL (normal <200 mg/dL). Repeated extensive microbiological and immunological investigations during previous admissions were negative or inconclusive. However, elevated triglyceride (246 mg/dL) and elevated IgA (1005 mg/dL) had also been documented previously.

During this admission, serum IgD was assayed and found to be polyclonal and increased, at 157 IU/mL (normal <100 IU/mL). Serum IgD remained elevated (287 IU/ml) while the child was asymptomatic. With the clinical suspicion of HIDS, sequencing of the exons and flanking intronic sequences of the mevalonate kinase (*MVK*) was performed. Sequencing revealed heterozygosity for two mutations, namely c.62C>T (p.Ala21Val) and c.372-

6T>C. Both mutations are novel, not described as known polymorphisms, and were absent on screening of 100 control subjects. While the alanine at position 21 is highly conserved across species, c.372-6T>C is expected to cause incorrect splicing. To determine their functional consequences, MVK enzyme activity was measured in cultured primary skin fibroblasts. Mevalonate kinase activity in patient's fibroblasts was 8 pmol/min/mg, compared to 467 pmol/min/mg in control fibroblasts. Based on these findings, a diagnosis of HIDS was made.

The child did not respond to therapy with prednisolone or non steroidal anti inflammatory drugs (NSAIDS), and developed severe rash when simvastatin was administered. Due to lack of affordability and unclear efficacy, etanercept or anakinra was not administered. The child continues to have recurrent symptoms, and has been re-admitted twice with hyperpyrexia and once with hip joint arthritis.

DISCUSSION

HIDS belongs to the group of hereditary periodic fevers, rare auto-inflammatory disorders characterized by intermittent self-limited inflammatory episodes with recurrent fever, synovial or serosal inflammation, rashes, uveitis or conjunctivitis, and, in some, amyloidosis [1]. HIDS is a rare autosomal recessive condition due to mutations in the *MVK* gene on chromosome 12q24 [1]. Only over 170 cases are known, mainly reported from Dutch or French kindreds [1, 2]. HIDS was secondary to different mutations in the only other report from India [3].

The diagnosis of HIDS can be confirmed by demonstrating low activity of *MVK* enzyme and/or disease-causing mutations in the *MVK* gene [2]. Most patients are compound heterozygotes for missense mutations in *MVK* gene, the most common being V337I, which is seen in >80% of cases [1]. Neither of the two nucleotide changes in the alleles of the *MVK* gene in our patient has been reported before [2]. Pathogenicity of these mutations was confirmed by the finding of a deficient *MVK* enzyme activity in cultured skin fibroblasts.

The mechanisms by which defects in the *MVK* gene cause a periodic inflammatory disease are unclear [4,5]. Abnormalities noted include increased levels of immunoglobulins (IgD, IgA), cytokines [interleukin (IL)-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-α], serum IL-1 receptor antagonist soluble TNF receptor, and urinary leukotriene E4 excretion [6]. The precise role of IgD in the pathogenesis has not yet been defined.

Unlike our patient, some patients with HIDS may develop neurological symptoms such as mental retardation, ataxia, and epilepsy, suggesting that mevalonic aciduria (MA, OMIM 251170) and HIDS form a continuous spectrum of abnormalities mediated by a deficiency of MVK enzyme activity [7]. Unlike in patients with MA, patients with HIDS have residual (1-8%) enzyme activity, as is confirmed in our patient [7, 8].

Consensus is lacking regarding how HIDS should be managed. Although HIDS is considered to be a benign condition, treatment is difficult and largely supportive. Anti-inflammatory drugs have variable efficacy in suppressing febrile attacks; relapses are unresponsive to steroids and only partially subdued by NSAIDS. Colchicine is suggested to be effective at prolonging intercritical remission periods without changing disease severity. Similarly, beneficial effects have been ascribed to therapy with simvastatin, an inhibitor of HMG-CoA reductase, anakinra, a recombinant interleukin-1 receptor antagonist, and etanercept, the tumour necrosis factor-α (TNF-α) inhibitor [9, 10]. More recently, demonstration of efficacy of zaragozic acid A suggests a role for modulation of isoprenoid biosynthesis in treatment of HIDS [4].

This report highlights the need to consider familial periodic fevers or auto-inflammatory disorders when evaluating patients with recurrent fever, synovial or serosal inflammation, rash, mucocutaneous manifestations and hepatosplenomegaly. HIDS should be considered as a differential diagnosis irrespective of family history and ethnicity.

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Mutation Analysis of Indian Patients with Urea Cycle Defects

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Molecular testing for a specific metabolic disorder remains the gold standard due to its high specificity and sensitivity and possibility of accurate prenatal diagnosis. We report four cases of urea cycle defect where mutational analysis of the involved genes was performed and subsequently, prenatal diagnosis could be offered to one of the family.

Key words: *Citrullinemia, Inborn errors of metabolism, Ornithine transcarbomylase deficiency.*

Urea cycle disorders (UCD) result from defects in the metabolism of the surplus nitrogen produced by the breakdown of protein and other nitrogen containing molecules. Newborns with a urea cycle disorder often appear normal during the first few days of life but rapidly develop hyperammonemic cerebral edema and related signs of lethargy, anorexia, hyperventilation or hypoventilation, hypothermia, seizures, abnormal posturing, and coma. In milder (or partial) urea cycle enzyme deficiencies, the first recognized clinical episode may be delayed for months, years or decades. Here,ammonia accumulation may be triggered by illness or stress at almost any time of life. These hyperammonemic episodes are marked by loss of appetite, cyclic vomiting, lethargy, and behavioral abnormalities. We herein report four cases of varying severity with various enzyme defects in urea cycle where molecular diagnosis later was helpful in counseling and prenatal diagnosis.

CASE REPORTS

Case 1: A six-year-old male child presented with developmental delay and seizures since the age of three months. His perinatal history was uneventful. Examination showed presence of microcephaly (Head circumference 49cm <3rd centile by NCHS), slurred speech, clumsiness while walking and writing. He had increased tone and brisk reflexes. His MRI showed cerebral atrophy. He had hyperammonemia (levels between 200-250 µmol/L, normal <80 µmol/L) intermittently for which he was on sodium benzoate therapy. Tandem mass spectroscopy showed high citrulline levels. Mutation analysis of the *ASS1* gene was carried out by direct DNA sequencing (ABI 3100, 4 capillary sequencer using Big dye terminator version 3.1 chemistry). It revealed a mutation p.Arg265Cys in a homozygous state. Unfortunately, the child developed intractable seizures, chronic encephalopathy which progressed to coma and death at 10 years of age.

Case 2: A four-day-old female born to a nonconsanguinous couple was admitted with neonatal encephalopathy on day three of life. There was history of previous sib death with similar complaints. Investigations of this child showed hyperammonemia (> 236 µmol/L) on several occasions without significant acidosis. Her tandem mass spectrometry (TMS) showed very high levels of citrulline (>5000µmol/L), urine thin layer chromatography also showed increased citrulline. She responded dramatically to ammonia lowering medications (Sodium benzoate) and peritoneal dialysis. Subsequently, child was lost to follow up but her DNA analysis of the *ASS1* gene showed the mutation p.Arg157His in a homozygous state with both parents being carriers for the same mutation.

Case 3: Another four day-old female child, a product of