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Mevalonate Kinase Deficiency as Cause of Periodic Fever in Two Siblings

Mevalonate kinase deficiency (MKD) is a rare autosomal recessive autoinflammatory disease caused by mutations in *MVK*. We report two siblings with MKD, presenting with recurrent febrile illnesses, detected to have compound heterozygous variants in *MVK*. MKD mimics common pediatric conditions and should be considered as a differential diagnosis.

Keywords: *Hyper-IgD syndrome, Pyrexia of unknown origin, Neonatal hepatitis, Periodic fever.*

Fever of unknown origin is often a diagnostic challenge in children. Etiology includes infections, malignancy, autoimmune and autoinflammatory diseases. Autoinflammatory diseases are multisystem disorders characterized by periodic attacks of fever and systemic inflammation. Mevalonate kinase deficiency (MKD) is an autosomal recessive autoinflammatory disease caused by mutations in the *mevalonate kinase* (*MVK*) gene which encodes for mevalonate kinase, a key enzyme in the mevalonic acid pathway [1]. The clinical spectrum ranges from Hyper-IgD syndrome (HIDS) (MIM 260920) to the more severe mevalonic aciduria (MIM 610377). This paper reports two siblings with MKD.

A five-year-old male child born to nonconsanguineous parents was symptomatic from 2 months of age with history of recurrent febrile illnesses associated with diarrhea, icterus, hepatosplenomegaly, along with thrombocytopenia and severe anemia requiring repeated blood and platelet transfusions. From 3 months of age he developed febrile episodes recurring weekly without any systemic focus, which subsided by 8 months of age. At 1.5 years of age, he developed frequent constipation with abdominal distention and pain which continued till 2.5 years of age. He developed recurrent tonsillitis and lymphadenopathy from four years of age. At five years, his height was 92 cm (-3.95 SD), weight 11.5 kg (-3.55 SD) and head circumference 46cm (-3.19 SD). He had a triangular face, open anterior fontanelle, blue sclera, cervical lymphadenopathy and hepatosplenomegaly (liver 4.5 cm and spleen tip palpable). Investigative work-up detected raised C-reactive protein (CRP) but other tests for infectious etiologies, immunodeficiency, chronic liver disease and storage disorders were negative. The proband's younger brother was also symptomatic at 1 month of age with fever, neonatal hepatitis, cholestasis and severe anemia. He also had elevated CRP levels even during asymptomatic periods. At 1 year of age he developed episodes of subacute intestinal obstruction and one episode of acute lymphadenitis. At 18 months of age his length was 68 cm (-5.3 SD), weight 6.5kg (-4.4 SD) and head circumference 43.5cm (-2.9 SD). He had a facial phenotype resumbling his brother's, cervical lymphadenopathy, hepatosplenomegaly (liver 5.5 cm and spleen 3.5 cm below costal margin) and motor and speech delay.

Repeated febrile episodes with elevated inflammatory markers raised the possibility of periodic fever syndrome. Urine organic acid analysis using gas chromatography and mass spectrometry (GCMS) showed elevated levels of mevalonolactone. Genetic testing using clinical exome panel by next generation sequencing in the proband revealed previously reported compound heterozygous variants, c.803T>C (p.Ile268Thr) on exon 9 and c.976G>A (p.Gly326Arg) on exon 10 in *MVK* gene (***Web Fig.* 1a**). Both the variants were confirmed in the second sibling (***Web Fig.* 1b**). Segregation analysis in parents could not be done. Both siblings were treated with tocilizumab. There was reduction in frequency of febrile episodes and normalization of CRP levels. Tocilizumab was discontinued due to adverse drug reactions and patients were shifted to nonsteroidal anti-inflammatory drugs (NSAID) and corticosteroids.

Approximately 300 cases of MKD have been reported with the vast majority having European ancestry (median age at diagnosis, 8 to 10 years) [2]. HIDS is characterized by recurrent febrile inflammatory episodes associated with diarrhea, abdominal pain, vomiting, lymphadenopathy, splenomegaly, macular papular rash, and arthritis. Additionally patients with mevalonic aciduria have intrauterine growth reduction, failure to thrive, facial

dysmorphism, and neurologic involvement [2]. Loss of function mutations in the *MVK* block the mevalonic acid pathway affecting protein prenylation and thereby decreasing geranylgeranyl pyrophosphate which leads to increased production of inflammatory cytokines [3,4].

Our patients initially had features of neonatal hepatitis with cholestasis followed by subacute intestinal obstruction probably caused by adhesions secondary to sterile peritonitis [1]. Elevated serum levels of polyclonal immunoglobulin D (IgD) is not diagnostic of MKD as it may be raised in tuberculosis, sarcoidosis, Hodgkin lymphoma and acquired immunodeficiency, or normal in 20% of cases [3]. IgD does not correlate with diseases severity or pathogenesis. IgD levels could not be measured in index case. Excretion of mevalonic acid in urine supports the diagnosis of MKD [1,3]. In mevalonic aciduria, mevalonolactone is significant and continuously observed unlike HIDS where it is mildly elevated or even normal in asymptomatic periods. Confirmatory diagnosis is possible by detecting homozygous or compound heterozygous mutations in *MVK* or decreased mevalonate kinase enzyme activity in lymphocytes or cultured fibroblasts. A strong clinical suspicion, urinary GCMS and genetic testing led to the confirmation of diagnosis at an early age in index patients. Both detected variants have been reported in patients with European and Arab ancestry [5,6]. The p.Ile268Thr variant is the second most common of over 200 variants found in patients with both MA and HIDS phenotypes [6]. This is the first report of these variants from India.

Acute exacerbations may be treated with NSAID and short course corticosteroids. Drugs like interleukin (IL) 1 blocking agents, anakinra and canakinumab, and anti TNF-α agent etanercept and IL-6 receptor antibody, tocilizumab, have also been successful in reducing the frequency of exacerbations [4]. However, cost and lack of availability of these medications limit their use in resource limited setting such as India.

HIDS is a self-limiting illness with poor quality of life but not associated with decreased life expectancy unlike severe form of mevalonic aciduria [2]. Prenatal genetic testing can be used to detect affected fetuses as there is 25 percent chance of recurrence in subsequent pregnancies.

This report highlights the fact that MKD is a disorder with constellation of commonly encountered symptoms and signs. Despite being rare, autoinflammatory disorders should be considered in the differential diagnosis of patients with recurrent febrile attacks associated with raised inflammatory markers. Genetic testing is a gold standard modality to confirm the diagnosis and end the diagnostic odyssey.

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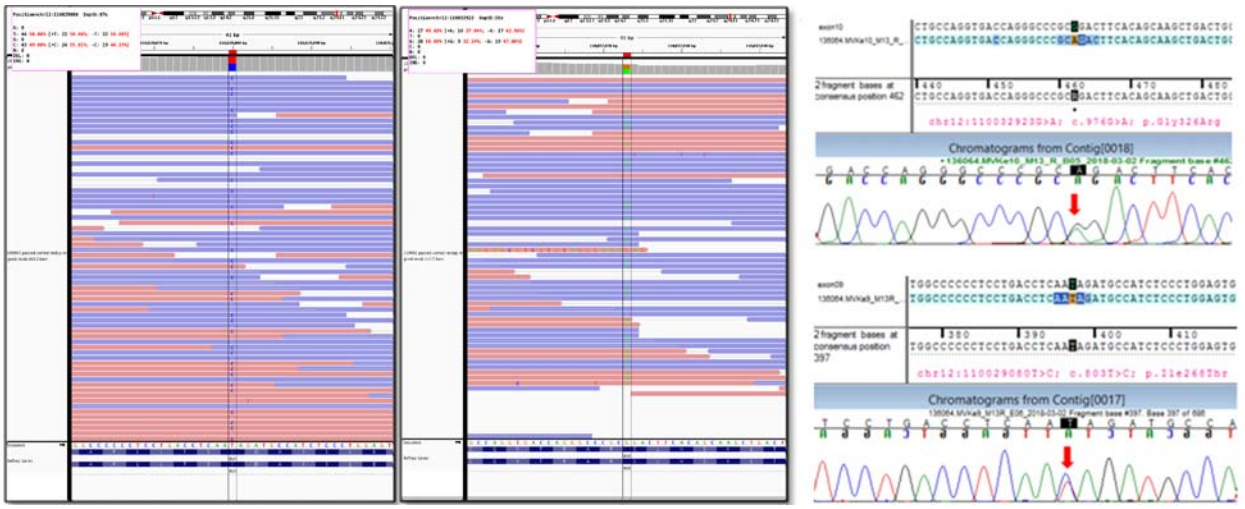

(*a*) (*b*)

WEB FIG. 1 *(a) Integrated genome viewer images of clinical exome sequencing showing compound heterozygous c.803T>C and c.976G>A variants for sibling 1 and (b) Electropherogram of respective variants for sibling 2.*