Mevalonic Aciduria in a Child Featuring Hepatic Fibrosis and Novel Mevalonate Kinase Mutations

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Abstract: Mevalonic aciduria (MVA) is an inborn error of isoprene biosynthesis caused by mevalonate kinase (MVK) gene mutations. Described below is a case of a Palestinian MVA patient suffering from prolonged fevers as well as from hepatic fibrosis - a rare feature of MVA. Also demonstrated is a unique genotype - heterozigosity of two novel MVK mutations; V8F (t25a), and F38I (t112a).

INTRODUCTION

Mevalonic aciduria (MVA) (OMIM 610377) is a rare inborn error of isoprene biosynthesis, caused by mutations in the mevalonate kinase (MVK) gene. MVA features recurrent febrile episodes, developmental delay, ataxia, dysmorphism, failure to thrive, cataracts, and retinal dystrophy [1]. MVK mutations are also responsible for the hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) (OMIM 260920) [1], an autosomal recessive disorder characterized by recurrent febrile episodes, abdominal pain, arthritis, rash and cervical lymphadenopathy [2].

Although HIDS and MVA are considered as separate clinical entities, many patients illustrate a phenotypic spectrum, possibly related to the level of enzyme activity. Mevalonate kinase activity is less severely impaired in HIDS patients compared to its activity in MVA patients [1]. Accordingly, mevalonate is excreted in the urine of HIDS patients in low-moderate levels and only during febrile episodes, while MVA patients continuously excrete high levels of mevalonate [3]. Moreover, specific genotypes are associated with resulting different mevalonate kinase activity levels, and thus with either HIDS or MVA [4].

Most of the reported HIDS and MVA patients are of western European descent [2]. However, cases have been reported of patients from countries including Portugal [5], Italy [6] and Turkey [7]. The first Palestinian HIDS patient was recently reported [8]. The diagnosis was made through evidence of elevated IgD levels, as well as by DNA sequencing demonstrating homozygosity of the MVK V377I mutation.

The following report describes a Palestinian child with hepatic fibrosis diagnosed with MVA, featuring novel mutations of the MVK gene.

CASE REPORT

A 1.5 year old Palestinian male was referred to our hospital from the GAZA strip for the investigation of hepatosplenomegaly. He is the third of four healthy children of non-consanguineous parents (Fig. 1A). Upon detailed history, he was found to have suffered from monthly episodes of fever up to 39° C, lasting 7-10 days, since the age of 10 weeks. In contrast to his normally developed twin sister, at the age of 1.5 years he was unable to stand, and did not use any meaningful words.

Physical examination revealed hepatomegaly, a maculopopular corporal and facial rash, and left elbow arthritis. Abdominal ultrasonography confirmed the presence of an enlarged heterogenic liver and a spleen of 9.5 X 8.6 cm. Portal blood flow was normal.

Neurological examination revealed general hypotonia and a linguistic developmental delay, otherwise being a normal examination.

No pathology was found in his retina, cornea, uvea or optic discs.

Venereal disease research laboratory (VDRL) tests, as well as serology for CMV, HSV, toxoplasma, hepatitis A, B and C were obtained and were all found negative. Serology tests for Rubella demonstrated an immunized individual.

Levels of immunoglobulins were tested and found to be mildly elevated: IgG 1980 mg/dL (N:420-1200), IgA 189 mg/dL (N:12-150), IgM 328 mg/dL (N:45-200). Complement levels were normal or mildly elevated. C-reactive protein level was 30 mg/dL. Serology for ANA, P-ANCA, C-ANCA, anti-LKM, anti-actin, ANF, anti-M2 and ASMA were all negative.

Liver biopsy was performed next and revealed an inflammatory lymphocytic infiltrate, associated with portal fibrosis (Fig. 2). Due to a thus suspected inflammatory-mediated condition, steroid therapy was begun. This treatment diminished both arthritis and fevers, although upon weeks of follow-up had little effect on the child's general...
well being. Upon the reduction of steroid dose, the fevers and arthritis reappeared. A trial of imuran treatment had no clinical effect.

Due to the combination of hepatosplenomegaly, recurrent fevers, and arthritis the diagnosis of MVA was considered and sought by urine organic-acid analysis. Mevalonate levels were 2250 mmol/mol Cr (N < 0.03) thus confirming the diagnosis. Levels of IgD, however, were only slightly elevated - 8.2 mg/dL (N 0-4.5). Genetic sequence analysis revealed the patient to be a compound heterozygote of two novel mutations on exon 1 of the MVK gene (Fig. 1C): V8F (t25a), and F38I (t112a). The patient's father was found to be the carrier of the V8F mutation (Fig. 1B). Hence the F38I mutation is most likely maternal in origin (DNA sample for sequencing was unavailable), or less likely, a de-novo mutation.

**DISCUSSION**

This case demonstrates the phenotypic continuum between MVA and HIDS; this patient presented with a mild
developmental delay, slightly elevated IgD blood levels and high urine mevalonate levels - all supporting diagnosis of MVA [1, 2]. Still, other features of MVA such as ataxia, dysmorphic features or cataracts [1] were absent, although none are considered to be sine qua non to MVA. One might argue that ataxia has not yet developed in this patient due to his young age, however, central cataracts and unusual facies have been previously described in MVA patients as young as 2 years of age [9].

One of the diagnostic challenges presented in this patient was the presence of hepatic fibrosis in liver biopsy, which temporarily shifted the differential diagnosis to more common inflammatory hepatic diseases. Although previously described in MVA patients [10], hepatic fibrosis is far from being considered a hallmark of the disease, and is scantily described in the literature, perhaps due to the infrequent exercise of liver biopsy in these patients.

Another remarkable finding in this patient was his genotype, as he was found to be a compound heterozygote of two novel MVK mutations: V8F (t25a), and F38I (t112a). Although mutations in MVK have previously been described in a HIDS patient of Palestinian descent [8], our reported case is, to our knowledge, the first described Palestinian MVA patient. In general the phenotypic severity of mevalonic aciduria correlates with the activity of the enzyme mevalonate kinase [1]. In the case described, the two novel mutations cause a change from an aliphatic (V,I) amino acid to an aromatic amino acid (V,F) and vice versa in the mevalonate kinase protein structure, thus affecting its activity.

As of now, medical treatment presents the principal challenge in MVA. Previously reported treatments including statins, the tumor necrosis factor alpha (TNF-α) inhibitor etanercept, and Anakinra, an interleukin-1 receptor antagonist [1] were all found to be of limited value. Recently, Neven, et al. [1] described a successful allogeneic bone marrow transplantation in an MVA patient. However, as this is a fairly new treatment, no evidence is present regarding its effect on neurological development.

In summary, this case highlights phenotypic features of MVA, such as hepatic fibrosis, and demonstrates the clinical spectrum of the disease. The reported unique genotype in this patient, as well as his unique ancestry, will hopefully enable earlier accurate diagnoses of future cases.

ABBREVIATIONS

ANA = Antinuclear antibodies
Anti-LKM = Anti-liver kidney microsomal antibodies
ANF = Antinuclear factor

Anti-M2 = Antimitochondrial protein 2
ASMA = Anti-smooth muscle antibodies
C-ANCA = Cytoplasmic antineutrophil cytoplasmic antibodies
CMV = Cytomegalovirus
HIDS = Hyperimmunoglobulinemia D and periodic fever syndrome
HSV = Herpes simplex virus
IgD = Immunoglobulin D
IgG = Immunoglobulin G
IgM = Immunoglobulin M
IgA = Immunoglobulin A
MVA = Mevalonic aciduria
MVK = Mevalonate kinase gene
P-ANCA = Perinuclear antineutrophil cytoplasmic antibodies
TNF-α = Tumor necrosis factor alpha
VDRL = Venerale disease research laboratory tests

REFERENCES