Molecular Genetics and Metabolism 104 (2012) 756–759

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Brief Communication

Severe phenotypic spectrum of mevalonate kinase deficiency with minimal mevalonic aciduria

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ARTICLE INFO

Article history:
Received 24 August 2012
Received in revised form 19 October 2012
Accepted 20 October 2012
Available online 24 October 2012

Keywords:
Mevalonate kinase deficiency
Failure to thrive
Hydrops
Hepatosplenomegaly
Lymphadenopathy
Autosomal recessive

ABSTRACT

Mevalonate kinase deficiency is a rare autosomal recessively inherited organic aciduria with a complex multi-systemic phenotype. We describe two deceased patients with clinically severe mevalonate kinase (MK) deficiency confirmed by *MK* mutation analysis. The phenotype in our patients ranged from neonatal hydrops in the first patient to severe failure to thrive, hepatosplenomegaly, recurrent febrile episodes and lymphadenopathy in the second. Both infants excreted relatively low amounts of mevalonic acid intermittently.

1. Introduction

Mevalonate kinase deficiency (OMIM# 610377) is caused by mutations in *MVK* that codes for mevalonate kinase (MK), the first committed enzyme in cholesterol biosynthesis (Fig. 1) [1–3]. It is a rate limiting step in isoprenoid biosynthesis which provides bioactive molecules that participate in cell growth, protein glycosylation and signal transduction processes [2,4–7]. The clinical spectrum of MK deficiency varies from severe MK deficiency to hyper IgD syndrome [3,8–14]. MK deficiency is an unusual organic aciduria with absence of hyperammonemia, metabolic acidosis or hypoglycemia [3,10]. There is an accumulation of mevalonic acid and mevalonolactone, relatively normal cholesterol levels in plasma, elevation of IgD in some patients, elevation of urinary leukotrienes, increased acute phase reactants, ESR, CRP and leukocytosis [5,8]. Dolichol, ubiquinone, isoprenoids and cholesterol, may be deficient [1,2,6,7,15]. MK deficiency causes a shortage of GGPP, a precursor for the isoprenylation of the small G proteins [16] which activates caspase I. This stimulates inflammatory attacks in MK deficiency by the increased interleukin-1β [17–20].

2. Clinical case reports

2.1. Case 1

The male infant of German non-consanguineous background was born at 27 weeks gestational age by Caesarian section to a 21 yr G3P1A1 mother. The pregnancy was complicated by massive fetal ascites and oligohydramnios at 25 weeks. Birth weight was 1170 g (50th centile), length was 35.5 cm (30th centile) and head circumference was 25.5 cm (50th centile). There was facial edema but no other dysmorphic features. He developed bronchopulmonary dysplasia, anemia, thrombocytopenia and infections (*Staphylococcus epidermidis* and suspected fungal), hepatosplenomegaly, jaundice and oliguric renal failure. Multiple transfusions of red cells and platelets, several anti-microbials and IVIG were given without benefit. Due to the worsening clinical course life support was withdrawn at 8 weeks.

2.2. Case 2

A 13 month old male born to a non-consanguineous 22 yr Polish mother and Scottish/French father was born at 37 wks with a birth weight of 2.4 kg (5th centile), length 48 cm (<3rd centile), and head circumference 33 cm (10th centile). In the neonatal period increased abdominal girth, hepatomegaly, direct hyperbilirubinemia and elevated liver enzymes were noted. Over the next year he developed severe failure to thrive, anemia, hypotonia, mild optic atrophy, cardiac hypertrophy,

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1096-7192/$ – see front matter.
http://dx.doi.org/10.1016/j.ymgme.2012.10.019

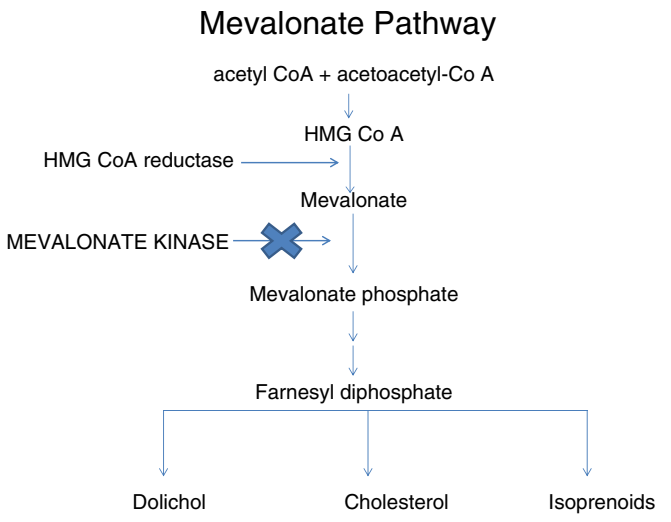

Fig. 1. Mevalonate kinase pathway.

hepatosplenomegaly, prominent abdominal veins, muscle wasting, proteinuria, rash and severe global developmental delay. Growth parameters remained far below the 3rd centile. He was irritable, had extreme emaciation, sparse hair, mild frontal bossing and slightly depressed nasal bridge (Figs. 2a–c).

At 21 months of age he was developmentally performing at 4 months of age. He had echogenic kidneys, proteinuria (>3 gm/liter), normal IgD 10 mg/L (ref range 0–140 mg/L) and cholesterol levels at 3.04 (<5.20 mmol/L). He had multiple hospitalizations due to viral infections (RSV and influenza A). Due to the recurrent episodes of fever, bilateral cervical, axillary and inguinal lymphadenopathy with morbilliform rash (Fig. 2b), swelling of knee and elbow joints, a clinical diagnosis of MK deficiency was considered despite the absence of mevalonic aciduria in urine organic acids on a few occasions. Management remained supportive. He died at age 2 years and 7 months of presumed sepsis.

3. Results

3.1. Case 1

3.1.1. Metabolic, pathological and molecular studies

Qualitative urine organic acid analysis was initially normal however a repeat analysis by stable isotopic dilution quantified mevalonic acid to be a concentration of 276 mg/g creatinine (analysis performed at the Kennedy Krieger Institute, Baltimore, MD) (Ref range 0.57 +/− 0.33 mg/g creatinine). Fibroblast MK activity was 0.1 (ref range 2.6–8.9 nmol/min/mg protein) indicating MK deficiency (performed at Oregon Health Sciences University). DNA analysis identified compound heterozygosity of R388X (HGMD accession number CM004007) and I268T (HGMD accession number CM990888) mutations.

3.2. Case 2

3.2.1. Metabolic, pathologic and molecular studies

There was generalized aminoaciduria and urine organic acids on qualitative analysis were initially normal. Quantitative analysis of a post mortem urine specimen by stable isotopic dilution determined the concentration of mevalonate to be 1220 mg/g creatinine (Ref range 0.57 +/− 0.33 mg/g creatinine). The skin fibroblasts had undetectable MK activity (ref range 2.6–8.9 nmol/min/mg protein). Respiratory chain enzyme assays of the muscle biopsy (Dr. Brian Robinson, Hospital for Sick Children, Toronto) showed reduced activities of

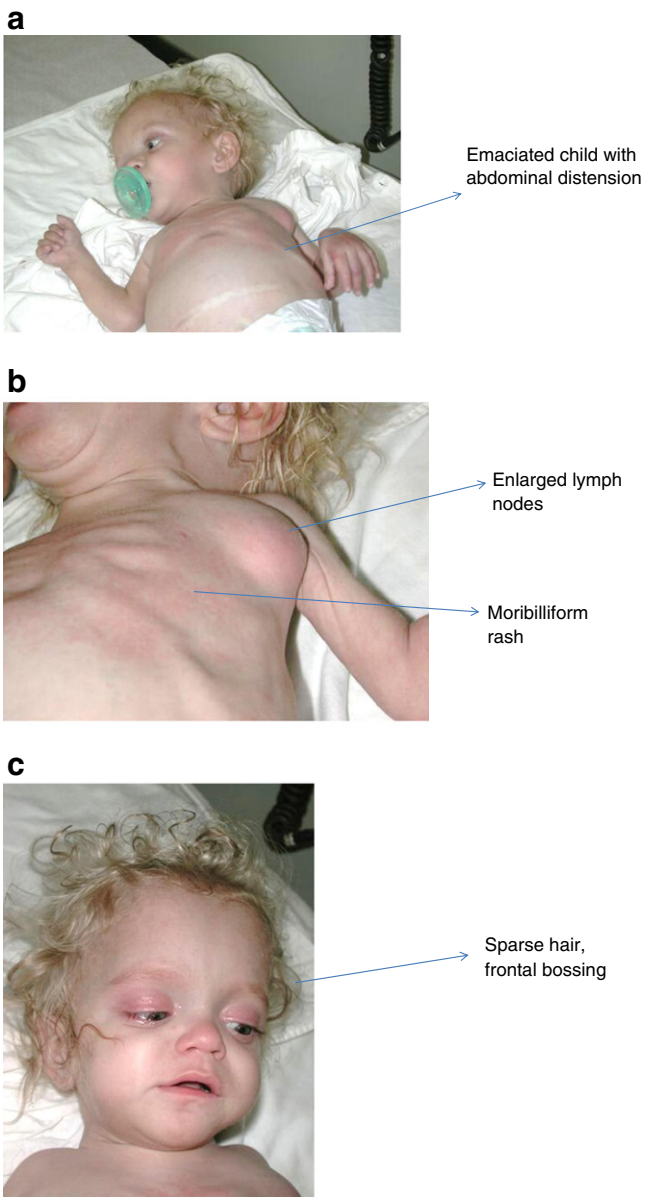

Fig. 2. a. Showing massive abdominal distension. b. Significant lymphadenopathy and morbilliform rash. c. Facial profile showing frontal bossing and sparse hair.

complexes I + III (10 nmol/min/mg tissue protein, ref range 45–170), complexes II + III (46 nmol/min/mg, ref range 56–162) and complex V (135 nmol/min/mg, ref range 294–1012), Citrate synthase and complex IV were within reference ranges. Muscle pathology and ultrastructural examination showed normal mitochondrial structure.

DNA analysis identified homozygosity for R388X (HGMD accession number CM004007) mutation.

4. Discussion

Both cases represent the severe end of the spectrum of MK deficiency. Case one presented with antenatal hydrops and case two was symptomatic from the perinatal period. Phenotypic features of severe MK deficiency can include hydrops, hepatosplenomegaly, cholestatic jaundice, recurrent fevers, morbilliform rash, arthralgia, lymphadenopathy, anemia, vomiting, diarrhea, facial dysmorphism, ataxia, hypotonia, cataracts and retinal involvement [3,4,17,21–25]. In both our patients the excretion of mevalonic acid was below the