

A Distinct Phenotype of Mevalonic Acidemia with Absence of Pathogenic Mutations of Mevalonate Kinase Gene

نمط ظاهري متميز لبيلة الميفالونيك مصاحبه بعدم وجود طفرات مرضيه في جين ميفالونات كيناز

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Abstract

Mevalonic aciduria is an autosomal recessive disorder caused by deficiency of mevalonate kinase and characterized by recurrent febrile crisis, ophthalmic and neurological manifestations. We report two brothers with mevalonic aciduria characterized clinically by severe failure to thrive, psychomotor retardation, dysmorphic features, retinitis pigmentosa and hypoplastic genitalia. Recurrent episodes of fever, a characteristic feature of mevalonic aciduria due to deficiency of mevalonate kinase enzyme was absent. Both patients excreted moderate amounts of mevalonic acid. Molecular analysis of *MVK* gene showed no abnormalities and plasma 7-dehydrocholesterol and serum immunoglobulin D were normal. This phenotype-genotype association has not been described in previous reports and future molecular genetic studies are required to know the full spectrum of disorders of the mevalonate pathway.

Keywords: mevalonic aciduria, mevalonate kinase, dysmorphic features, retinitis pigmentosa.

ملخص

تبين الحالتان الموصوفتان أعراضاً فريدة لمرض وراثي نادر يسمى (مرض ارتفاع الحمض الميفالوني (بيلة الميفالونيك). المريضان لم يشكوا من ارتفاع متكرر في درجات الحرارة الذي يميز مرض ارتفاع الحمض الميفالوني الناتج من نقص أنزيم ميفالونات كيناز، وبفحص الجين المسبب للمرض لم يثبت وجود طفرة؛ مما يؤشر لضرورة عمل فحص جينات متطور؛ لمعرفة الطفرات النادرة للمرض، وقد تكون هذه الأعراض مؤشراً لمعرفة مرض جديد.

الكلمات المفتاحية: بيلة الميفالونيك، ميفالونات كيناز، ميزات تشوه، التهاب الشبكية الصباغي.

Introduction

Mevalonic aciduria (MVA, OMIM 251170) is a rare autosomal recessive disorder caused by deficiency of mevalonate kinase (MVK) and identified as the first defect in cholesterol biosynthesis (Bretón Martínez, JR. & *et al.* 2007; 829). At least 30 patients with MVA have been reported (Haas, D. Hoffmann, GF. 2006; 13). It is characterized by psychomotor retardation, hypotonia, dysmorphic features, failure to thrive, progressive cerebellar ataxia, progressive visual impairment and recurrent febrile crisis that are commonly accompanied by hepatosplenomegaly, lymphadenopathy, abdominal symptoms, arthralgia and skin rash. (Haas, D. Hoffmann, GF. 2006; 13), (Poll-The, BT. & *et al.* 2000; 363-366).

Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS, OMIM 260920) is an autosomal recessive disorder characterized by recurrent episodes of fever associated with lymphadenopathy, arthralgia, gastrointestinal dismay and elevated level of serum immunoglobulin D. (Tsimaratos, M. & *et al.* 2001; 413-414). MVA is an unusual organic aciduria with absence of hyperammonemia, metabolic acidosis or hypoglycemia (Prasad, C. & *et al.* 2012; 756-759). Mutations in the *MVK* gene and reduced activity of the MVK enzyme have been identified as underlying cause of both MVA and HIDS syndrome. (Bretón Martínez, & JR. *et al.* 2007; 829). (Houten, SM. & *et al.* 2000; 367-370). We report

two brothers who had persistent mevalonic aciduria manifesting with psychomotor retardation, failure to thrive, dysmorphic features, progressive visual loss and hypoplastic genitalia. However, both patients did not have recurrent febrile crisis, hepatosplenomegaly or lymphadenopathy. Genetic analysis of *MVK* gene showed no abnormalities. We hypothesize that future genetic testing for disorders of the mevalonate pathway including enzymes distal to the mevalonate kinase enzyme will help in identifying the etiology of this phenotype (Gibson, KM. & *et al.* 1997; 391-394).

Case reports

Patient 1

A 6 year old male born to consanguineous Palestinian parents (first cousins) at term after uneventful pregnancy with a birth weight of 2.9 kg (10th centile). The length and head circumference at birth were not known. He was hospitalized at the age of 1 year due to severe failure to thrive, microcephaly, hypotonia, developmental delay, dysmorphic features and hypoplastic genitalia. His weight was 6.6 kg, length 66 cm and head circumference 41 cm, all were far below the 3rd centile. He had long eyelashes, thick eyebrows, sparse hair and thin philtrum [Figure 1]. Ophthalmic examination showed bilateral pigmentary retinopathy, optic atrophy and poor vision. Genital exam showed penile length of 1 cm (<3rd centile), hypoplastic scrotum and small retractile testes.

He had multiple hospitalizations due to severe failure to thrive, psychomotor retardation and hypotonia. At the age of 6 years, his weight was 8.5 kg, length 90 cm head circumference 43.5 cm. He had absent eye contact, severe axial hypotonia and limbs spasticity.

Laboratory findings

Qualitative urine organic acid analysis by gas chromatography-mass spectrometry (GC-MS) on three occasions showed large excretion of mevalonic acid. DNA analysis of *MVK* gene did not demonstrate pathogenic mutations (analysis performed at Laboratory Genetic

Metabolic Disease, University of Amsterdam academic centre, Netherlands). Genetic testing for Fragile X syndrome showed no abnormalities. Serum IgD, IgA and plasma 7DHC were normal. Other normal studies included karyotyping, plasma very long-chain fatty acids (VLCFA), plasma ammonia, lactic acid, plasma amino acid analysis, serum biotinidase enzyme assay and transferring isoelectric focusing. Muscle biopsy showed normal enzymatic activity of mitochondrial respiratory chain complexes I-V. Magnetic resonance imaging of the brain showed no abnormalities.

Patient 2

4 year old male, the younger brother of patient 1. Was born by cesarean section due to breech presentation after uneventful pregnancy, Birth weight 2.3 kg (<3rd centile). The length and head circumference at birth were also unknown. He was hospitalized at the age of 1 year for severe failure to thrive, developmental delay, hypotonia, pigmentary retinopathy and, dysmorphic features [Figure 2a] and hypogonadism [FIG.2b]; a phenotype which appeared identical to his brother. Over the next 3 years, his growth parameters remained far below the 3rd centile. At the age of 4 years, he also had absent eye contact, severe axial hypotonia and limb spasticity.

Laboratory findings

Qualitative urine organic acid analysis by GC-MS on two occasions also showed large excretion of mevalonic acid. Magnetic resonance imaging of the brain showed mild cortical atrophy and quadri- ventricular dilatation. Serum IgD and IgA levels were normal. Plasma cholesterol was normal and 7DHC was 0.89 µg/ml (normal < 2 µg/ml and in patients with Smith-Lemli-Opitz syndrome > 10 µg/ml). karyotyping was normal. Other normal tests included normal plasma aldosterone, 17-hydroxyprogesterone and plasma cortisol response to ACTH stimulation test.

Discussion

Both patients had distinct phenotype characterized by hypoplastic genitalia, severe failure to thrive, microcephaly, psychomotor retardation and pigmentary retinopathy with characteristic absence of recurrent febrile crisis, hepatosplenomegaly and lymphadenopathy. Despite the finding of persistent excretion of mevalonic acid in both patients, molecular analysis of *MVK* gene in patient one did not demonstrate pathogenic mutations. We hypothesize that the lack of genotype phenotype correlation in our patients suggests that deficiency of an enzyme in the mevalonate pathway other than *MVK* may be responsible for this phenotype and the need for advanced genetic testing as whole Exome Sequencing to identify the pathogenic mutations in the mevalonate pathway.

Similar to what is observed in MVA, patients with HIDS typically present with recurrent episodic fevers, lymphadenopathy, abdominal pain, diarrhea, arthralgia and rash. (Haas, D. Hoffmann, GF. 2006. 13); (Poll-The, BT. & *et al.* 2000, 363-366). While a distinctive laboratory finding in HIDS is a constitutively elevated level of serum IgD, it was normal in our patients.

Three patients with mevalonic aciduria with atypical presentations were reported; Two siblings had ataxia as the predominant clinical manifestations with increasing age and the third patient, a 6-year old boy presented at the age of 5 years with cerebellar ataxia and retinal dystrophy (Prietsch, V. & *et al.* 2003; 258-261). Similar to our patients, he has never developed febrile crisis and levels of IgD were repeatedly normal. Unlike our patients, all the 3 patients had pathogenic mutations of the *MVK* gene (Prietsch, V. & *et al.* 2003; 258-261).

Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive, multiple malformation, mental retardation syndrome (Correa-Cerro, LS. Porter, LD. 2005; 112-126). It's clinical presentation is extremely variable but typical facial features include microcephaly, bitemporal narrowing, Ptosis, anteverted nares, cleft palate and micrognathia. (Nwokoro, NA. & *et al.* 2001; 105-119). The biochemical findings of

increased plasma 7DHC and decreased cholesterol levels led to identification of mutations in *DHCR7* gene. Patient two had normal 7DHC and cholesterol levels so we did not perform genetic analysis of *DHCR7* gene.

In animal cells, the cholesterol biosynthetic pathway contains a unique series of three sequential ATP-dependent enzymes that convert mevalonate to isopentenyl diphosphate: MVK, phosphomevalonate kinase (PMK) and mevalonate 5-diphosphate decarboxylase (MDD). The later plays an important role in regulating cholesterol biosynthesis which was studied through incubation with various synthetic substrate analogs and characterization of mutant enzymes (Qiu, Y. & *et al.* 2007; 6164-6168). The authors are unaware of any human phenotype caused by deficiency of PMK or MDD.

The block of the mevalonate pathway induces programmed cell death and mitochondrial dysfunction. The effects of selected isoprenoid compounds as Phytol, Geranylgeraniol and Lycopene on programmed cell death were studied. The percentage of programmed cell death was significantly reduced after Phytol and Geranylgeraniol treatment but was not affected with Lycopene.^[12] The authors speculated that exogenous isoprenoids could be potential novel therapeutic tools for the still orphan drug disease mevalonate kinase deficiency (MKD) (Tricarico, PM. & *et al.* 2014; 6843-6856).

In response to exogenous cholesterol, the major feedback inhibitor of isoprenoid biosynthesis, growth velocities of MKD fibroblasts declined in comparison with control cells, further suggesting an impairment of non-sterol isoprenoid biosynthesis in MKD (Hoffmann, GF. & *et al.* 1997; 541-546).

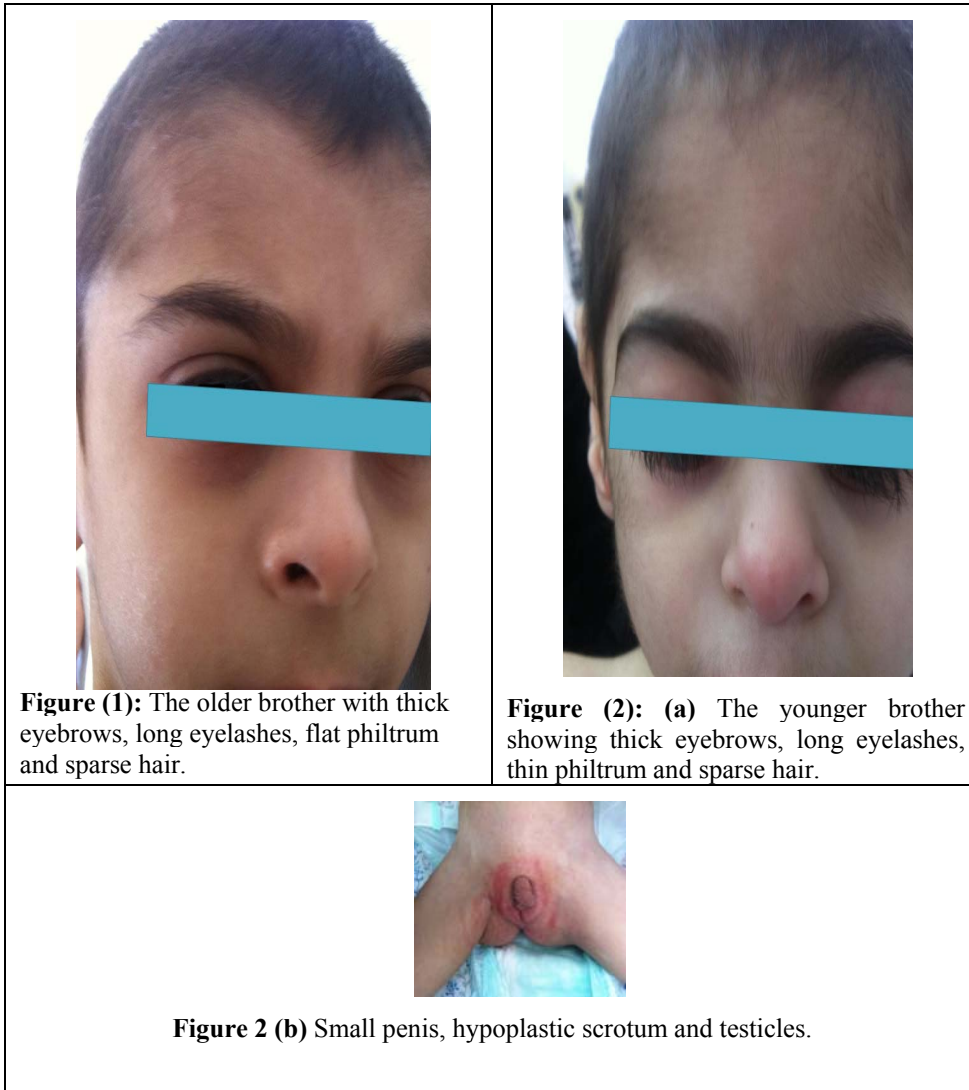
The atypical phenotype in our patients correlates with the absence of pathogenic mutations of *MVK* gene. Whether this phenotype is due to deficiency of an enzyme in the mevalonate pathway distal to *MVK* or caused by a rare mutation not identified by gene sequencing and require advanced genetic testing which may further expand the clinical,



biochemical and genetic spectrum needs to be further studied in future reports.

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