

Mevalonate kinase deficiency

Evidence for a phenotypic continuum

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Abstract—Both mevalonic aciduria, characterized by psychomotor retardation, cerebellar ataxia, recurrent fever attacks, and death in early childhood, and hyper-immunoglobulin D (hyper-IgD) syndrome, with recurrent fever attacks without neurologic symptoms, are caused by a functional deficiency of mevalonate kinase. In a systematic review of known mevalonate kinase-deficient patients, the authors identified five adults with phenotypic overlap between these two syndromes, which argues for a continuous spectrum of disease. Mevalonate kinase deficiency should be considered in adult patients with fitting neurologic symptoms, with or without periodic fever attacks.

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Mevalonate kinase deficiency, caused by mutations in the mevalonate kinase gene, is associated with two disparate clinical syndromes. The hyper-immunoglobulin D (hyper-IgD) and periodic fever syndrome (HIDS; MIM 260920) is an autoinflammatory disease characterized by lifelong recurrent episodes of fever, abdominal distress, lymphadenopathy, and skin rash,^{1–3} which usually start in the first year of life. There are no apparent neurologic or morphologic abnormalities, and in between the febrile attacks, patients are remarkably free of symptoms. Mevalonic aciduria (MVA; MIM 251170) is typically a disease of infantile onset, characterized by psychomotor retardation, ataxia, failure to thrive, cataracts, and dysmorphic features.^{4,5} Patients also experience periodic fever attacks, similar to but more severe than in HIDS, and in general they die in early childhood.

Mevalonate kinase, which phosphorylates mevalonic acid, is a central enzyme in the isoprenoid pathway; end-products include cholesterol, dolichol, and ubiquinone. This pathway is also responsible for isoprenylation, a posttranslational modification of proteins causing them to become membrane bound. How a defect in this metabolic pathway leads to either of the clinical phenotypes is obscure.

(Random) clinical observation of these patients suggests that the clinical presentation of mevalonate kinase deficiency represents a phenotypic continuum from MVA to HIDS, instead of two separate phenotypic

entities. To test this observation, we searched our clinics and database to identify (adult) mevalonate kinase-deficient patients with neurologic signs and symptoms.

Methods. *Patients.* The Nijmegen International HIDS Registry⁶ consists of 81 patients with metabolically and/or genetically confirmed mevalonate kinase deficiency. On screening of this registry, four patients with neurologic signs were identified. One additional patient with MVA and mevalonate kinase deficiency was identified through the neurology clinics. Some of the patients have been described earlier.^{6,8} For comparison, we also summarize the clinical data from 32 patients with classic HIDS without neurologic signs and symptoms in the HIDS Registry, for whom all genetic and metabolic data were available. Patients 1, 2, and 4 were examined by us. Patients 3 and 5 had been examined by others.

Analysis of mevalonate kinase gene mutations, enzyme activity, and urinary mevalonic acid. Genomic DNA was extracted from whole blood or Epstein–Barr-immortalized lymphoblasts from the patients, and the mevalonate kinase gene was amplified and sequenced according to established protocols.² For analysis of mevalonate kinase enzyme activity, we employed a radiometric assay using extracts of cultured lymphoblasts.⁸ Proton NMR spectroscopy (500 MHz) was used to quantify mevalonic acid in urine at pH 2.5, from samples outside fever attacks. Under these conditions, mevalonic acid gives a singlet resonance at 1.33 ppm, whereas in some patients, also the lactone of mevalonic acid may be observed as a 1.37-ppm resonance.

Results. A summary of clinical symptoms and test results is presented in the table; see the supplementary material in the *Neurology* Web site for detailed case descriptions (go to www.neurology.org). All patients were of Dutch descent, and except for Patients 1 and 2, who were brothers, the family history of the patients was negative. In all five patients, the first symptoms appeared within the first year of life. Four of the five patients had recurrent fever episodes with characteristic accompanying symptoms such as abdominal distress, lymphadenopathy, erythematous skin rash, aphthous ulcers, and arthralgia.

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Table Comparison of patient characteristics

Characteristics	Patients					Hyper-IgD syndrome,* n = 32	Mevalonic aciduria,† n = 11
	1	2	3	4	5		
Current age, y	45	44	30‡	54	41	31 (11–58)	4 (0.5–12)
Gender, M/F	M	M	F	M	F	16/16	5/6
Clinical characteristics							
Periodic fever attacks	+	+	+	–	+	+	+
Mental retardation	+	+	+	++	++	–	+ / + +
Language disorder	+	+	?	+	?	–	?
Cerebellar ataxia	+	+	–	+	+	–	+ / – (5/10)
Ocular symptoms§	+	+	–	+	+	–	+ / – (6/11)
Epilepsy	–	–	+	–	+	–	–
Age at onset, mo	0	0	6	12	6	3 (0–96)	ND
IgD, IU/mL	680	1,170	304	20	465	880 (376–5,300)	ND
Mevalonate kinase mutations	V377I/W62X	V377I/W62X	P167L/G202R	A334T/H20P	A334T/W62X	12 different mutations	ND
Mevalonate kinase enzyme activity,¶ %	ND	4.5	1.8	1.1	< 0.5	10.5 (2–32)	1.5 (0–4)
Mevalonic acid in urine,** mmol/mol creatinine	4	15.4	Raised††	2,730	7,200	ND	10,850 (1,700–56,000)

* Data from all patients in the Nijmegen International HIDS Registry who fulfilled the following criteria: no neurologic symptoms, known mutations in the mevalonate kinase gene, and known deficient mevalonate kinase enzyme activity. Results presented as medians (range).

† Data from 11 mevalonic aciduria patients described by Hoffmann et al.⁴ Four of them had died before age 4. Results presented as medians (range).

‡ Age at death.

§ Ocular symptoms include cataracts and progressive tapetoretinal degeneration.

|| Serum concentration of immunoglobulin D (IgD), normal <100 IU/mL.

¶ Mevalonate kinase enzyme activity, measured in Epstein–Barr-virus transformed lymphoblasts, expressed as percentage of controls.

** Mevalonic acid concentration in urine, normally undetectable.

†† No quantitative data available.

ND = not determined.

Patient 4 never experienced such fever episodes. This patient had a normal IgD concentration. Three patients had mild to moderate mental retardation and two had severe mental retardation; all patients except for Patient 3 were institutionalized. The three patients examined by us exhibited a similar language disorder: grammatically simple language with a strong predominance of nouns and adjectives, echolalia, palilalia, phonemic paraphasias, and omission of the first consonant in words. Four of five patients had cerebellar ataxia, more pronounced in gait than in the arms. One patient had left temporal epilepsy with complex partial seizures; one other patient had generalized tonic-clonic seizures. The ocular symptoms in four of the five patients included progressive blindness due to tapetoretinal degeneration and cataracts. Patients 1 and 2 both had hearing loss, presumably due to frequent ear infections and mastoiditis. Generalized muscle hypotonia was observed in Patient 4, with normal nerve conduction studies. Figure E-1 in the supplementary material on the *Neurology* Web site shows severe cerebellar atrophy in Patient 4. Patient 1 was reported to have had a left hemispheric ischemic stroke of unknown etiology at age 40 but had recovered with only a very mild residual clumsiness. Patient 3 died at age 30 after a brief intercurrent illness,

diagnosed as staphylococcal pneumonia; autopsy was not performed. The other four patients are still alive.

Discussion. The patients presented herein, who all have mevalonate kinase deficiency, illustrate a phenotypic continuum between HIDS and MVA. Four of five experience characteristic episodes of fever and inflammation, though, intriguingly, one patient did not. All have mental retardation with additional neurologic signs in a varying degree of severity, such as cerebellar ataxia, epilepsy, and a language disorder that may or may not be specific for the disease. We were unable to determine how this language disorder compares with language deficits in patients with mental retardation of other causes. All patients have survived to adulthood; one patient died at age 30, owing to intercurrent pneumonia.

This is in sharp contrast to what has been described in the literature on classic MVA. One study describes the phenotype of 11 patients with MVA.⁴ The most severely affected had profound developmental delay, dysmorphic features, cataracts, hepatosplenomegaly, lymphadenopathy, and anemia and

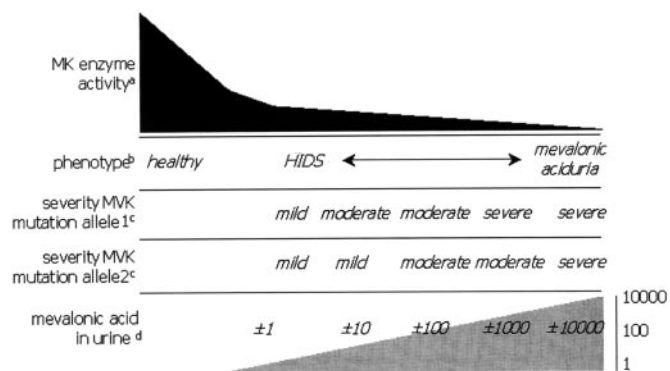


Figure 1. Proposed genotype–phenotype spectrum for mevalonate kinase (MK) deficiency. (a) Mevalonate kinase enzyme activity, ranging from 100% (left) to <1% (right). (b) Phenotype associated with decreasing enzyme activity; double-headed arrow depicts continuous phenotypic spectrum between two extremes (hyper-immunoglobulin D and periodic fever syndrome and mevalonic aciduria). (c) Genotype consists of a combination of mild (e.g., V377I), moderate (e.g., H20P, I268T), and severe (e.g., A334T) mutations in mevalonate kinase gene (MVK). (d) Concentration of mevalonic acid detected in urine samples, average estimates, expressed in mmol/mol of creatinine.

died in infancy. Less severely affected patients had psychomotor retardation, myopathy, and ataxia. All patients had recurrent crises with fever and lymphadenopathy. The authors did not find a relation between the neurologic phenotype and the remaining enzymatic activity.⁴ Another report of four young patients illustrated that both MVA and HIDS are caused by mevalonate kinase deficiency.⁹ Unfortunately, no genotypes were offered by either of these reports. Patients surviving to their sixth decade, such as our Patient 4, have never been described. The patients described here seem to bridge the gap between the classic MVA and HIDS phenotypes. Mevalonate kinase deficiency should be considered in adult patients with fitting neurologic symptoms, with or without periodic fever attacks.

In figure 1, a phenotypic spectrum of MVA/HIDS is proposed. One explanation for the varying degree in severity of phenotype might be the specific genotype involved. Generally, patients are compound heterozygous for two different mutations in the mevalonate kinase gene. These mutations may have a different effect on the function of the enzyme, some leading to a minor loss of efficiency (e.g., V377I), others causing near complete loss of function (e.g., A334T). The resulting sum of the residual enzyme activities and efficiency may account for the phenotypic variability (see figure 1).

But genotype analysis alone is unable to explain the remarkable variability in phenotype. In a study of three MVA patients,¹⁰ one patient was included with a mild phenotype, still alive at age 20 with a genotype identical to our Patient 4. In contrast, one other patient in that report, who was homozygous for

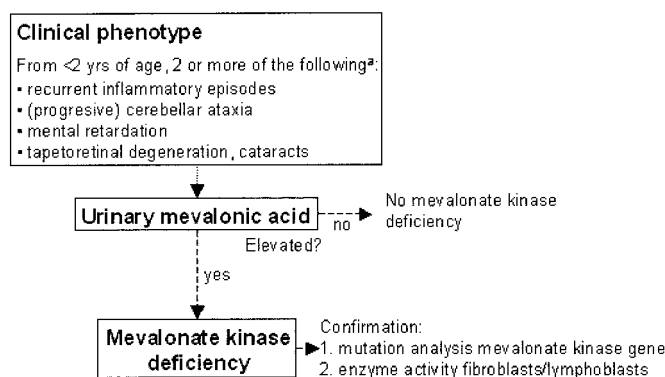


Figure 2. Screening for mevalonate kinase deficiency. Screening would be recommended in cases with two or more of these symptoms (a), starting from an early age; also cases of recurrent inflammatory episodes without other symptoms. It can most directly be done by measuring urinary mevalonic acid concentration. When this is elevated, further diagnostic procedures can be performed for confirmation: 1) mutation analysis of mevalonate kinase gene: relatively easy and available; 2) enzyme activity measurement: most direct confirmation but available only in specialist research setting. Data on sensitivity or specificity of these tests are lacking.

the I268T mutation, was severely affected and died in the first year of life. We have previously described two adult brothers with this genotype who have HIDS without any neurologic symptoms.⁸ Therefore, genetic trans-acting or environmental factors have to be considered to explain the phenotypic variability.

Measurement of urinary mevalonic acid by mass spectrometry or proton NMR spectroscopy is the most straightforward step to screen for mevalonate kinase deficiency (figure 2). Serum IgD is not always elevated in mevalonate kinase deficiency, and as illustrated by Case 4, normal values do not exclude the diagnosis.³

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