# THE NATURAL HISTORY OF MEDIUM-CHAIN ACYL COA DEHYDROGENASE DEFICIENCY IN THE NETHERLANDS: CLINICAL PRESENTATION AND OUTCOME

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**Objectives** To describe the clinical presentation and long-term follow-up of a large cohort of patients with medium-chain acyl-CoA dehydrogenase (MCAD) deficiency.

**Study design** A nationwide, retrospective analysis of clinical presentation and follow-up in 155 Dutch patients with MCAD deficiency.

**Results** Most patients presented between 3 months and 5.1 years of age; 13% had symptoms as neonates not exclusively related to breast-feeding. An acute presentation before the diagnosis was made resulted in a mortality of 22% (25/114), whereas 21% (19/89) developed disabilities after the diagnosis. On follow-up, a total of 44 patients reported fatigue (35%; 28/80), muscle pain (31%; 25/80), and/or reduced exercise tolerance (39%; 31/80). Cardiac evaluation in 11 adult patients revealed no abnormalities in cardiac function explaining these complaints. Children with MCAD deficiency readily become overweight.

**Conclusions** Mortality and morbidity were high in undiagnosed children with MCAD deficiency; establishment of the diagnosis significantly improves outcome. Strikingly, after the diagnosis and initiation of treatment, overweight and chronic complaints (fatigue, muscle pain, and reduced exercise tolerance) were prominent. *(J Pediatr 2006;148:665-70)*

Inherited disorders of mitochondrial fatty acid oxidation (mFAO) compose a group of acute life-threatening disorders, of which medium-chain acyl coenzyme A dehydrogenase (MCAD [E.C.1.3.99.3; MIM 201450]) deficiency is considered the most common.[1] The MCAD enzyme is responsible for the first step in mitochondrial $\beta$-oxidation of CoA esters of medium-chain fatty acids.

Since the first description of a patient with MCAD deficiency in 1976 by Gregersen et al,[2] several case reports and reports of groups of patients have been published.[3-8] Usually, clinical presentation of MCAD deficiency is related to fasting and increased metabolic stress, which precipitate acute symptoms such as drowsiness or lethargy that may develop into coma or even sudden death. Although most patients present during early infancy, some case reports have described neonatal[9-13] and adult presentations.[14-18] Depending on the study design, most studies reported high mortality (16% to 26%) and considerable morbidity after an acute metabolic derangement in undiagnosed patients. Wilson et al[8] showed that establishing the diagnosis improves outcome in children with MCAD deficiency.

Detection of acylcarnitines in blood using tandem mass spectrometry has evolved into a screening test for MCAD deficiency with high sensitivity and specificity in the newborn period.[19,20] In several areas, MCAD deficiency is currently under evaluation or already implemented for neonatal population screening. Consequently, an understanding of the natural history of MCAD deficient patients has become necessary.[21] Data on follow-up until adulthood are not available. We describe a retrospective, nationwide analysis of the natural history in 155 patients with MCAD deficiency, with follow-up until adulthood in 32 patients.

| | | | |
|---|---|---|---|
| CPT | Carnitine palmitoyltransferase | MCAD | Medium-chain acyl-CoA dehydrogenase |
| CRF | Case record form | mFAO | Mitochondrial fatty acid oxidation |
| ECG | Electrocardiography | | |

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**Table I. Genetic analysis of the ACADM gene performed in 99 Dutch families with MCAD deficiency**

| Allele 1 | | | Allele 2 | | | No. of families |
|---|---|---|---|---|---|---|
| nucleotide change | exon | coding effect | nucleotide change | exon | coding effect | |
| c.85C>T | 1 | p.R29X | c.985A>G | 11 | p.K329E | 1 |
| c.157C>T | 3 | p.R53C | c.985A>G | 11 | p.K329E | 2 |
| c.233T>C | 4 | p.I78T | c.233T>C | 4 | p.I78T | 1 |
| c.233T>C | 4 | p.I78T | Not identified | | | 1 |
| c.351A>C | 5 | p.T117T | c.985A>G | 11 | p.K329E | 1 |
| c.395C>G | 6 | p.P132R | c.985A>G | 11 | p.K329E | 1 |
| c.609A>C | 8 | p.L203F | c.985A>G | 11 | p.K329E | 1 |
| c.789A>C | 9 | p.L263F | c.985A>G | 11 | p.K329E | 1 |
| c.985A>G | 11 | p.K329E | c.985A>G | 11 | p.K329E | 86 |
| c.985A>G | 11 | p.K329E | Not determined | | | 4 |

Nucleotide numbering starts from the first adenine of the ATG translation initiation codon of the *ACADM* cDNA sequence. Amino acid numbering starts from the methionine encoded by the ATG translation initiation codon of the *ACADM* cDNA sequence.

## METHODS

The Medical Ethical Committee of the University Medical Center Groningen (MEC 98/04/075) approved the study protocol. In The Netherlands, medical care for patients with a metabolic disorder is restricted to the metabolic divisions of pediatric departments in the 8 university hospitals. To perform a national analysis of MCAD-deficient patients, we contacted all of these divisions and their affiliated metabolic laboratories, all of which provided information on their patients with known MCAD deficiency. In The Netherlands, the first patient with MCAD deficiency was diagnosed in the late 1970s. Data for all patients diagnosed after this first patient and before July 2003, including clinical history, laboratory data, family history, and data on follow-up after diagnosis, were documented in case record forms (CRFs). The clinical history could be reconstructed in collaboration with the responsible clinicians from each family. CRFs were anonymously archived in a database and used to describe the genetic epidemiologic characteristics.[22]

Subjects included in this study were diagnosed with MCAD deficiency after an MCAD enzyme assay and/or MCAD DNA analysis had confirmed the diagnosis. Subjects also were included when hypoketotic hypoglycemia was found combined with the specific pattern of urinary organic acids and/or plasma acylcarnitines and a positive MCAD enzyme assay and/or MCAD DNA analysis was confirmed in a family member. The initial laboratory indication for the diagnosis of MCAD deficiency was based on either urinary organic acid analysis using gas chromatography–mass spectrometry (increased concentrations of *N*-hexanoic-, *N*-suberic-, and dicarboxylic acids) and/or plasma acylcarnitine profile (increased concentrations of octanoylcarnitine, decanoylcarnitine, and decenoylcarnitine).

To determine the outcome after the diagnosis of MCAD deficiency, all CRFs were independently reassessed by 2 investigators. Based on the descriptions in the medical files and discussions with responsible clinicians, 1 chapter of the CRF contained data on motor, mental, and social functioning, including information on housing of the subjects. Severe disability was defined as either impairment in motor, mental, and social functioning or a combined impairment leading to institutionalization. Mild disability was defined as any other reported impairment in functioning. Differences in scoring the CRFs and final results were discussed with a third investigator (GPAS).

A questionnaire was sent to parents of children with MCAD deficiency, containing questions about the presence or absence of the following complaints: fatigue, muscle pain, reduced exercise tolerance, and problems after ingestion of dietary fat. The children's weight and height were measured during regular hospital visits using standard anthropometric techniques. Measurements were compared with Dutch reference data reported by Gerver and de Bruin.[23]

Cardiac investigations were performed in a subset of adult patients. The investigations included 12-lead electrocardiography (ECG), 24-hour ECG Holter monitoring, echocardiographic examination, and troponin measurements. Findings were compared with normal values reported previously.[24]

Statistical analysis was performed using SPSS version 11.0 software (SPSS Inc, Chicago, Il). Differences between groups of patients were analyzed using nonparametric tests. Differences were considered statistically significant at $P < .05$.

## RESULTS

### Genotype in Dutch Families With MCAD Deficiency

Genetic analysis of the *ACADM* gene (MIM 607008) performed in 99 of 110 Dutch families with MCAD deficiency revealed 8 different mutations, of which the c.985A>G mutations is by far the most common, followed by the c.233T>C mutation (Table I). Subjects of 4 families were analyzed only for the presence of the c.985A>G mutation and found to be heterozygous. In 1 family, sequencing of the entire *ACADM* gene revealed only 1 heterozygous c.233T>C mutation, although the subjects clearly demonstrated MCAD deficiency at the enzymatic level.