3-hydroxy-3-methylglutaryl-CoA synthase deficiency

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Introduction

Overview

Deficiency of mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase, the rate-limiting enzyme in hepatic ketogenesis, causes potentially life-threatening hypoglycemic hypoketotic coma during fasting periods. In the normal, nonfasting state, patients are completely asymptomatic and show no abnormalities in standard metabolic tests. As a consequence, diagnosing 3-hydroxy-3-methylglutaryl-CoA synthase deficiency has been thought to be difficult, and despite the life-threatening nature of the disease it may remain unrecognized in at least some patients. The author explains that the disease should be easy to recognize when adequate samples are obtained in the acute crisis. The diagnosis is confirmed through mutation analysis in the HMGCS2 gene on chromosome 1p12.

Key points

- HMG-CoA synthase is required for the generation of ketone bodies that provide chemical energy to the brain and other organs at times of fasting.
- The genetic deficiency of HMG-CoA synthase can lead to hypoglycemia, coma, and probably death at times of fasting, but has no known adverse effects outside fasting periods.
- The diagnosis is based on biochemical findings during fasting periods and is confirmed through mutation analysis.
- Treatment is restricted to avoidance of prolonged fasting periods; no other (drug) treatment is indicated.

Historical note and terminology

A genetic deficiency of mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (protein abbreviation HMCS2, EC 2.3.3.10) as a cause of fasting hypoketotic coma in a child was first recognized in 1997 (Thompson et al 1997) and has since been reported in a number of additional patients (Morris et al 1998; Aledo et al 2001; Aledo et al 2006; Bouchard et al 2001; Zschocke et al 2002; Wolf et al 2003). Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase has to be distinguished from its cytosolic isoform, which catalyses the rate-limiting first step of cholesterol biosynthesis and is encoded by a different gene. The gene for mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase is located on chromosome 1p12. The full cDNA sequence and gene structure were identified by 1997 (Boukaftane et al 1994; Mascaro et al 1995; Boukaftane and Mitchell 1997). The crystal structure of human mitochondrial HMG-CoA synthase was published in 2010 (Shafkat et al 2010). Guidelines for the diagnosis of mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency were published in 2002 (Zschocke et al 2002).

Clinical manifestations

Presentation and course

Clinical symptoms caused by mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency are those of acute hypoglycemia. Patients show unexpected deterioration of consciousness and rapidly deepening coma leading to respiratory arrest during prolonged periods of poor food intake or fasting. The condition may present at any age but the first symptomatic episode is usually in late infancy due to greater intervals between meals in conjunction with a higher incidence of common infections with fever, vomiting, and reduced food intake.

Prognosis and complications
The prognosis is excellent provided that fasting is avoided.

**Clinical vignette**

An affected boy was the first child of unrelated German parents [Aledo et al. 2001]. After an unremarkable neonatal and early infantile period, at 11 months of age, he developed gastroenteritis with vomiting and poor feeding. On the third day of this illness he suddenly deteriorated with coma and respiratory arrest. Blood glucose after resuscitation was 1.2 mmol/l (norm: >3 mmol/l). Apart from elevated transaminases (aspartate aminotransferase 283 U/l, norm: 10-27 U/l; alanine aminotransferase 138 U/l, norm: 5-23 U/l) and lactate dehydrogenase (1502 U/l, norm: 200-500 U/l), there were no abnormalities in routine clinical chemical analysis. Urinary organic acid analysis revealed massive dicarboxylic aciduria without adequate ketonuria. Acylcarnitines analyses in dried blood spots were normal. The patient recovered well with intravenous glucose infusion.

Enzyme studies in fibroblasts showed normal beta-oxidation capacity. Unfortunately, free fatty acids and ketone bodies had not been measured at the time of the acute decompensation, and it was felt necessary to perform a monitored fasting test under controlled conditions in a metabolic hospital unit. During this test the boy developed hypoglycemia (blood glucose 2.3 mmol/l) much earlier than envisaged, 12 hours after the last meal. At this time there was massive elevation of plasma free fatty acids (3290 µmol/l, norm: <300) without concomitant elevation of total plasma ketones (174 µmol/l, norm: <150, in prolonged fasting: >1500). Blood lactate, insulin and transaminases were within normal ranges. Urinary organic acids again showed massive dicarboxylic aciduria without adequate ketonuria. Acylcarnitines in dried blood spots were normal.

The diagnosis was later confirmed by molecular studies that revealed compound heterozygosity for the mutations G212R (c.634G>A) in exon 3 and R500H (c.1499G>A) in exon 9 of the *HMGCS2* gene. The family was advised to avoid fasting periods of more than 6 to 8 hours. There were no subsequent hypoglycemic episodes, and the child has developed normally with no residual neurologic impairment.

**Biological basis**

**Etiology and pathogenesis**

Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency is an autosomal recessive disorder caused by mutations in the *HMGCS2* gene. This gene stretches over 20 kb on chromosome 1p13-p12 and contains 10 exons. So far, 26 different mutations (20 predicted missense, 3 nonsense, 1 splice, 1 frameshift, and 1 large deletion) in affected patients have been reported and are listed in the *HMGCS2* mutation database ([Lanthaler et al. 2014](#); [Pitt et al. 2015](#)). Functional analyses showed complete loss of protein or protein function in most mutations studied ([Ramos et al. 2013](#)). Four German and English patients from 3 independent families were compound heterozygous for the same mutation p.G212R (c.634G>A, exon 3) and different second mutations; thus, it is possible that p.G212R is a prevalent mutation in persons of European descent.

Fasting is accompanied by an increased breakdown of fatty acid stores for provision of energy to peripheral tissues. Humans are unable to convert even-chain fatty acids into glucose, and organs such as the brain and muscle that do not have the enzymes for complete fatty acid oxidation rely on the utilization of the ketone bodies acetoacetate and 3-hydroxybutyrate during fasting. The hepatic biosynthesis of acetoacetate from acetoacetyl-CoA involves a 2-step process catalyzed by the enzymes 3-hydroxy-3-methylglutaryl-CoA synthase and 3-hydroxy-3-methylglutaryl-CoA lyase. The latter enzyme is also required for the breakdown of the amino acid leucine, and 3-hydroxy-3-methylglutaryl-CoA lyase deficiency usually presents as an organic aciduria with acute metabolic (keto-) acidosis, hypoglycemia, liver disease, and sometimes fatal Reye syndrome-like crisis. In contrast, mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase appears to be required only for ketogenesis during fasting. A deficiency of this enzyme, therefore, only leads to symptoms or metabolic abnormalities during fasting or poor food intake.

**Epidemiology**

This disease has been rarely diagnosed, and most patients appear to have been identified in a few centers that are well aware of the clinical presentation and laboratory findings. Considering that affected patients show typical development and no metabolic abnormalities except during fasting periods, the condition may be underdiagnosed. Aledo and colleagues reported 2 affected siblings, 1 of whom had suffered an episode with extreme lethargy following a vomiting illness. The boy improved with intravenous glucose, but no diagnosis was made until his brother presented
with severe hypoglycemic coma (Aledo et al 2006). This report supports the suggestion that despite the life-threatening nature of the disease, it remains unrecognized in at least some patients.

**Prevention**

The enzyme deficiency itself is of genetic origin and cannot be prevented. However, hypoketotic hypoglycemia and its complications may be completely prevented by avoiding fasting periods greater than 6 to 8 hours in infants and small children. It can be assumed that fasting tolerance is greater in older children, but no systematic data are available to support or refute this assumption.

**Differential diagnosis**

The clinical presentation of mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase with hypoketotic hypoglycemia resembles that of the disorders of mitochondrial fatty acid oxidation, particularly medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. However, these disorders can usually be recognized by metabolic abnormalities in the interval. For example, disorders of long-chain fatty acid oxidation may also show additional features such as cardiomyopathy, muscle disease or liver disease. The fasting tolerance in mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase may be shorter than in medium-chain acyl-CoA dehydrogenase deficiency.

**Diagnostic workup**

Diagnosing mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency rests on the examination of adequate samples obtained during hypoglycemia (Zschocke et al 2002). It is essential to recognize deficient conversion of free fatty acids to ketones by measuring these substances in serum. 3-hydroxybutyrate is sufficient for the assessment of ketogenesis capacity as it usually accounts for over two-thirds of total ketones and is more stable than acetoacetate. During prolonged fasting, free fatty acids and total ketones typically reach concentrations of 1500 µmol/ml or higher, with ketones usually exceeding free fatty acids. Insufficient ketogenesis in this situation (eg, ratio free fatty acids / ketones >2) is pathognomonic for a deficiency of mitochondrial beta-oxidation or ketogenesis even if ketones are elevated compared to the fed state. The discrepancy between highly elevated free fatty acids and low ketones is most pronounced in mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency where the ratio may exceed 20.

Once hypoketosis is recognized, the combination of normal acylcarnitines in dried blood spots (some compounds may be elevated as is normal during fasting) and a “fasting pattern without ketones” in urinary organic acids is sufficient to diagnose mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency with virtual certainty, provided that the samples were obtained during the acute episode. Though acylcarnitine profiles in most patients were reported as normal, Aledo and colleagues found strongly increased concentrations of acetyl-(C2)-carnitine after carnitine supplementation in 1 patient (Aledo et al 2006). High C2-carnitine in combination with low total carnitine may also be found in the acute crisis. Careful examination of the urinary organic acid profile obtained from the acute presentation may show highly increased concentrations of 4-hydroxy-6-methyl-2-pyrone. Although this metabolite may also be elevated in some ketotic patients, it is highly suggestive for mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency. This observation led to the diagnosis of 7 additional patients from various parts of the world in a single Australian center (Pitt et al 2015).

Molecular studies are used for the confirmation of the diagnosis. DNA analysis should involve full sequencing of the coding region as well as genomic quantification as the disease has been caused by larger deletions in several patients (Pitt et al 2015). No metabolic abnormalities are usually present in the fed state in mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency, and enzyme studies not only require liver biopsy but are hampered by the cytosolic isoenzyme. A fasting test may be helpful but is potentially dangerous and should be carried out in a specialist hospital setting only.

**Management**

Management rests on avoidance of fasting periods greater than 6 to 8 hours in infants and small children. Fasting tolerance is thought to be greater in older children and adults. No additional measures are necessary. Specifically, there is no evidence that administration of carnitine is of benefit.

**Special considerations**
Pregnancy

Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency is not thought to be associated with complications of pregnancy providing that prolonged fasting is avoided.

Anesthesia

Great care should be taken that prolonged fasting is avoided prior to, during, and after surgery.

References cited


**References especially recommended by the author or editor for general reading.

ICD and OMIM codes

ICD codes
ICD-9:
Unspecified disorder of metabolism: 277.9

ICD-10:
Metabolic disorder, unspecified: E88.9

OMIM numbers
3-hydroxy-3-methylglutaryl-CoA synthase 2, mitochondrial: *600234

Profile

Age range of presentation
0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance
male=female

Family history
family history may be obtained
family history typical

Heredity
autosomal recessive

Population groups selectively affected
none selectively affected

Occupation groups selectively affected
none

Differential diagnosis list
disorders of mitochondrial fatty acid oxidation
medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
disorders of long-chain fatty acid oxidation
cardiomyopathy
muscle disease
liver disease

Associated disorders
comahypoglycemia

Other topics to consider
HMG-CoA lyase deficiency
Hypoglycemia
Medium-chain acyl-CoA dehydrogenase deficiency
Mitochondrial disorders

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