2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency

Stefan Kolker MD (Dr. Kolker of University Children's Hospital Heidelberg has no relevant financial relationships to disclose.)
Tyler Reimschisel MD, editor. (Dr. Reimschisel of Vanderbilt University has received contracted research grants from Shire.)

Originally released July 3, 2005; last updated November 21, 2018; expires November 21, 2021

Introduction

This article includes discussion of 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency, 17beta-hydroxysteroid dehydrogenase type 10 deficiency, HSD10 deficiency, and MHBD deficiency. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency, also denoted 17beta-hydroxysteroid dehydrogenase type 10 (HSD10) deficiency, is a rare X-linked organic aciduria with a highly unusual neurodegenerative disease course involving progressive loss of acquired mental and motor skills, loss of vision, and medically intractable epilepsy in early childhood. There are also patients with a more severe neonatal presentation that may mimic a mitochondrial disease as well as patients without neurologic symptoms despite complete loss of enzyme function. The author reports that modulation of HSD10, which binds to and interacts with amyloid-beta peptide and exacerbates its toxicity, has been identified as a novel therapeutic strategy for Alzheimer disease. Furthermore, HSD10 expression in colorectal cancer altering mtDNA content and energy metabolism in cancer cells was shown to predict survival.

Key points

- 2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency is a progressive multisystem disease resembling mitochondrial disorders.
- It is caused by mutations in the HSD17B10 gene, which codes for a multifunctional protein; the pathogenesis of the condition is poorly understood.
- Inheritance is X-chromosomal, with severe symptoms in males and variable or no symptoms in females.
- The predominant clinical features are progressive severe neurologic symptoms and cardiomyopathy; onset is at birth or in the first years of life.
- There is no effective treatment.

Historical note and terminology

2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency, also denoted 17beta-hydroxysteroid dehydrogenase type 10 (HSD10) deficiency, is an X-linked organic aciduria first described in 2000 (Zschocke et al 2000).

Meanwhile, some additional patients (mostly males) have been identified (Ensenauer et al 2002; Olpin et al 2002; Sutton et al 2003; García-Villoria et al 2004; Poll-The et al 2004; Sass et al 2004). The disease is caused by mutations in HSD17B10 (previously denoted HADH2), which is located on the X chromosome (Ofman et al 2003). Identification of this gene also opened a new approach to the understanding of the pathogenesis. The protein encoded by the HSD17B10 gene, correctly denoted HSD10, had been reported to be involved in the pathogenesis of Alzheimer disease (Yan et al 1997) and is now known to be identical to MRPP2, an essential component of the mitochondrial ribonuclease P (Holzmann et al 2008).

Clinical manifestations

Presentation and course

A limited number of patients with 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency have been diagnosed to date, and it is unlikely that the full spectrum of clinical phenotypes is known. The condition is X-linked and predominantly affects boys. Pathogenic mutations that completely abolish enzyme activity often cause a less severe
clinical phenotype than those associated with residual enzymatic activity in hemizygous males. Notably, complete loss of 2-methyl-3-hydroxybutyryl-CoA dehydrogenase activity was not associated with neurologic symptoms in several male patients in one family, supporting the notion that the severity of the clinical presentation might not correlate with the degree of enzyme deficiency (Rauschenberger et al 2010). Heterozygous females may present with variable, usually nonprogressive, intellectual disability depending on hepatic X-inactivation patterns. Affected boys often show mild, nonspecific developmental delays in the first year of life, and lactic acidosis is frequently found. Progressive deterioration typically starts between 6 and 18 months. Patients start to lose acquired psychomotor skills and develop progressive neurologic anomalies including loss of vision, epilepsy, dystonia, or spasticity. Furthermore, severe cardiomyopathy is common. Brain MRI may reveal progressive, variable changes, including cerebral atrophy and infarctions. Patients often die during infancy, but may reach school age or even adulthood. Two patients already died during the newborn period (Ensenauer et al 2002; Olpin et al 2002; Sutton et al 2003; Poll-The et al 2004; Sass et al 2004).

One 7-year-old girl with 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency has been reported who showed nonprogressive psychomotor retardation, normal eye findings, and discrete changes on an MRI of the brain (Ensenauer et al 2002). In addition, affected females may have hearing loss or hearing impairment (García-Villoria et al 2004). There are also several heterozygous females (including mothers of affected boys) without clinical symptoms or with only mild learning difficulties.

**Prognosis and complications**

The prognosis in boys with 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency is poor. No effective treatment is known. Prognosis in affected females depends on the hepatic X-inactivation pattern and is variable. The degree of psychomotor impairment cannot be predicted in heterozygous females diagnosed before birth.

**Clinical vignette**

The index patient reported in 2000 was the first child of an unrelated German couple and was born at term. On the second day of life he developed tachydyspnea and metabolic acidosis with severe hypoglycemia (0.17 mmol/L), elevated lactate (11.6 mmol/L), mild hyperammonemia (210 µmol/L), and ketonuria. Seizure-like movements were observed but stopped without treatment. The child recovered under intravenous glucose infusion; no diagnosis was made at that stage. Subsequent development showed mild psychomotor delay. The boy achieved head control at the age of 4 months and sat with support at 8 months. At the age of 13 months he moved by rolling from side to side and was able to sit by himself and stand when held by both hands. Expressive and receptive language as well as cognitive development was delayed, though emotional reactions were appropriate for age. After 14 months of age, coinciding with a vaccination, he started to show progressive loss of motor skills. He lost the ability to stand or sit and developed marked restlessness and choreoathetoid movements. Visual contact was lost, and ophthalmologic investigations indicated non-pigmentary retinal degeneration verging on blindness and normal nerve conduction latency. Acoustic evoked potentials were normal. During the next weeks the child developed seizures in the form of repeated head dropping and a modified hypsarrhythmia-pattern on EEG. Treatment with vigabatrin reduced the frequency of seizures but the boy did not become seizure-free. A brain MRI revealed slight frontotemporal atrophy without significant changes in the basal ganglia or white matter. At 2 years of age, the boy had severe intellectual impairment, choreoathetoid movements, absence of directed hand movements, marked hypotonia, and minimal reaction to external stimuli. The subsequent course was characterized by severe epilepsy that was resistant to antiepileptic treatment. The boy died at 3.5 years of age in status epilepticus.

**Biological basis**

**Etiology and pathogenesis**

2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency is an X-linked disorder caused by mutations in the **HSD17B10** gene. This gene stretches over 3.1 kb on chromosome Xp11.2 and contains 6 exons. Remarkably, the same missense mutation p.Arg130Cys in exon 4 of the **HSD17B10** gene is found in approximately half of the reported families; other missense mutations are found in other families. One missense mutation p.Gln165His that completely removes enzyme function has been reported to not be associated with neurologic symptoms.

The mutated protein is multifunctional with different names (reflecting different function), which in view of its structure
is best denoted HSD10. The clinical features of its deficiency are fundamentally different from other disorders of isoleucine breakdown. The deficiency of 2-methylbutyryl-CoA dehydrogenase (the first beta-oxidation step of 2-methylated short acyl-CoA compounds) may be a benign coincidental finding. The deficiency of the last reaction of isoleucine breakdown, 2-methylacetoacetyl-CoA thiolase, may give rise to the same metabolite spectrum in urinary acid analysis but presents as a ketolysis defect due to the role of this enzyme in ketone body utilization. It is, therefore, likely that enzyme functions outside the isoleucine catabolic pathway are responsible for the clinical features. Patients with 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency frequently show elevated concentrations of lactate in blood and cerebrospinal fluid indicative of a disturbance of energy metabolism. A reduced activity of the mitochondrial respiratory chain complex I was demonstrated in muscle (Ensenauer et al 2002). Multiple oxidative phosphorylation (OXPHOS) deficiency (complexes 1, 3, 4, and 5) was demonstrated in heart and liver tissue (Chatfield et al 2015). Mitochondrial energy failure predominantly affecting the brain and heart thus may best explain the clinical phenotype.

The neurologic disease manifestations show some similarities to neurodegenerative disorders of adulthood such as Alzheimer disease where mitochondrial dysfunction is thought to contribute to progressive apoptotic neuronal loss (Andersen 2004). Interestingly, HSD10 is thought to play an important role in the pathogenesis of Alzheimer disease (Yan et al 1997).

Loss-of-function and rescue experiments in Xenopus embryos and cells derived from conditional Hsd17b10−/− knockout mice (Rauschenberger et al 2010) demonstrate that HSD10 is essential for structural and functional integrity of mitochondria independently of its 2-methyl-3-hydroxybutyryl-CoA dehydrogenase activity.

The effect of HSD10 on mitochondrial integrity and function is best explained by HSD10 being identical to MRPP2, one of the 3 proteins that form the mitochondrial ribonuclease P (RNase P) complex (Holzmann et al 2008). Mitochondrial RNase P initiates posttranscriptional processing of large polycistronic RNAs deriving from mitochondrial DNA (mtDNA) transcription by cleavage of the mtDNA-encoded precursor RNA at the 5′ start site of tRNAs. Subsequent cleavage at the 3′ end by RNase Z produces mature tRNAs and thereby releases protein-coding mRNAs of subunits for complexes 1, 3, 4, and 5 (Holzmann et al 2008; Chatfield et al 2015). In addition, MRPP1 and MRPP2 together also function as a tRNA:m1R9methyltransferase, stabilizing 19 of 22 mitochondrial tRNAs by methylation (Vilardo et al 2012). This explains why HSD10 deficiency causes a primary mitochondrial disorder. Mitochondrial RNase P was found to be compensatorily upregulated in muscle OXPHOS function, but not in heart tissue (Chatfield et al 2015). In patient fibroblast and HSD10-deficient mice, decreased HSD10 (ie, MRPP2) concentration was associated with MRPP1 protein concentration, indicating that HSD10 is important to maintain normal MRPP1 protein levels. Ectopic HSD10 expression partially restored RNA processing and MRPP1 expression in these models (Deutschmann et al 2014).

In Alzheimer disease, HSD10 acts as a binding site for amyloid-beta peptide inside the mitochondrial matrix, thereby exacerbating amyloid-beta peptide-induced toxicity. Therefore, HSD10 is often termed “amyloid-binding alcohol dehydrogenase” (ABAD) in this context. The binding of and interaction between these 2 proteins triggers a cascade of events, finally resulting in mitochondrial dysfunction. Therefore, pharmacological modulation of ABAD/HSD10 (eg, by benzothiazole-based ureas) has become a potential therapeutic strategy for Alzheimer disease (Hroch et al 2016).

In colorectal cancer, loss of HSD10 expression was found to be associated with poor prognosis (Amberger et al 2016). This finding suggests that HSD10 plays a role in altering the energy metabolism of colorectal cancer via modification of the mtDNA content. Therefore, HSD10 analysis might be an important marker predicting survival for this disease.

**Epidemiology**

The rare disease has so far been reported only in persons of European descent but is most likely not restricted to European and North American populations.

**Prevention**

The disease cannot be prevented. It may be recognized by prenatal diagnosis when the mutation is known in a family.

**Differential diagnosis**

The progressive neurodegenerative disease course may resemble a lysosomal storage disorder but the correct diagnosis should be easily found by urinary organic acid analysis. The pattern of urinary metabolites may resemble
mitochondrial acetoacetyl-CoA thiolase deficiency because 2-methylacetoacetate, which is typically for the latter condition, is unstable and may be degraded. Marked differences in the clinical picture between the 2 conditions, particularly in affected boys, usually become obvious in the second year of life.

**Diagnostic workup**

The most important diagnostic investigation is the analysis of organic acids in a urine sample by gas chromatography-mass spectroscopy. All patients described so far excrete large amounts of 2-methyl-3-hydroxybutyric acid and tiglylglycine, precursor metabolites in the isoleucine catabolic pathway. 2-methylacetoacetate is not detectable in urine; this substance is indicative of mitochondrial acetoacetyl-CoA thiolase deficiency but is unstable. 2-ethylhydracrylic acid has been reported as a sensitive biochemical marker in heterozygous females (García-Villoria et al 2009). Acylcarnitine profiling usually shows normal results. However, elevated C5:1 carnitine levels were reported in 2 Japanese siblings (hemizygous for p.Ala157Val) (Akagawa et al 2017). The diagnosis may be confirmed by enzyme analysis in leucocytes or fibroblasts or by mutation analysis that may be performed in genomic DNA. Prenatal diagnosis is best carried out by mutation analysis.

**Management**

Management is symptomatic; no curative treatment is known. Dietary restriction of the precursor amino acid isoleucine is not of apparent benefit.

**Special considerations**

**Pregnancy**

There is little experience with regard to pregnancy outcome in heterozygous women who have biochemical abnormalities.

**References cited**


Chatfield KC, Coughlin CR 2nd, Friederich MW, et al. Mitochondrial energy failure in HSD10 disease is due to defective mtDNA transcript processing. Mitochondrion 2015;21:1-10.** PMID 25575635


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

Former authors

Johannes Zschocke MD PhD

ICD and OMIM codes

ICD codes

ICD-9:
Disturbances of branched-chain amino-acid metabolism: 270.3

ICD-10:
Other disorders of amino-acid metabolism: E71.1

OMIM numbers

2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency: #300438

Profile

Age range of presentation

0-01 month
01-23 months
02-05 years

Sex preponderance
male>female, >1:1
male>female, >2:1

Family history
family history may be obtained
family history typical

Heredity
sex-linked variable/milder presentation in females

Population groups selectively affected
none selectively affected

Occupation groups selectively affected
none selectively affected

Differential diagnosis list
lysosomal storage disorders
mitochondrial acetoacetyl-CoA thiolase deficiency

Associated disorders
epilepsy
blindness
deafness

Other topics to consider
Alzheimer disease
Epilepsy
Intellectual disability