Ethylmalonic encephalopathy and SCAD deficiency

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Introduction

This article includes discussion of ethylmalonic encephalopathy, SCAD deficiency, ethylmalonic aciduria, ethylmalonic encephalopathy, SCADH deficiency, and short-chain acyl-CoA dehydrogenase deficiency. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Ethylmalonic encephalopathy is a devastating, infantile, autosomal recessive, metabolic disorder caused by defects in the mitochondrial sulfur dioxygenase, ETHE1, and characterized by ethylmalonic and methylsuccinic aciduria, lactic acidemia associated with developmental delay, orthostatic acrocyanosis, recurrent petechiae, chronic diarrhea, and abnormalities on brain MRI. The authors also report on an alternative treatment option for ethylmalonic encephalopathy.

Short-chain acyl-CoA dehydrogenase deficiency, a defect in the mitochondrial beta-oxidation pathway, also leads to ethylmalonic aciduria, but only variable symptoms have occurred in a few patients. Thus, it remains a poorly defined entity exhibiting a wide clinical spectrum. The authors report a variety of clinical phenotypes from mostly asymptomatic individuals to individuals with brain malformations and infantile spasms. In addition to disruptive mutations, several prevalent polymorphic variations in the SCAD gene may lead to variable elevations of ethylmalonic acid in the urine, again with uncertain clinical relevance. New insights on involved pathomechanisms as the role of mitochondrial dysfunction and the potential role of novel molecular analyses in the diagnostic procedure are highlighted.

Key points

• Ethylmalonic encephalopathy is a progressive, often fatal neurometabolic disorder characterized by ethylmalonic and methylsuccinic aciduria and lactic acidemia.
• It is associated with developmental delay, acrocyanosis, petechiae, and chronic diarrhea.
• Ethylmalonic encephalopathy is caused by mutations in the ETHE1 gene, a mitochondrial sulfur dioxygenase involved in the catabolism of sulfide that accumulates to toxic levels in ethylmalonic encephalopathy.
• Clinical symptoms ascribed to SCAD deficiency may be reflective of ascertainment bias. Alternatively, early identification and treatment may prevent complications that may have occurred due to interaction between genetic susceptibility and other genetic factors or environmental stressors. Likely, SCAD deficiency is mostly solely a biochemical phenotype without clinical manifestations.

Historical note and terminology

Ethylmalonic encephalopathy (MIM 602473) is a neurometabolic disorder characterized by ethylmalonic and methylsuccinic aciduria, lactic acidemia associated with developmental delay, acrocyanosis, petechiae, and chronic diarrhea. The underlying metabolic defect was identified in a mitochondrial matrix protein. Hoffmann and colleagues first described this inborn error of metabolism as ethylmalonic aciduria (Hoffmann et al 1990). Since the initial report, less than 50 cases have been described worldwide, suggesting that the disorder may be very rare (Tiranti and Zeviani 2013).
Short-chain acyl-CoA (butyryl-CoA) dehydrogenase (SCAD) deficiency (MIM 201470) is a defect in the mitochondrial beta-oxidation pathway. The deficient enzyme, short-chain acyl-CoA dehydrogenase (EC 1.3.99.2), is the first enzyme of the intramitochondrial beta-oxidation spiral catalyzing the dehydrogenation of C4 and C6 fatty acids. The first report of symptomatic SCAD deficiency was done by Turnbull and colleagues (Turnbull et al 1984). The impaired metabolism of short-chain CoAs leads to short-chain dicarboxylic aciduria (ethylmalonic and adipic acids) and increased C4 species on an acylcarnitine profile.

**Clinical manifestations**

**Presentation and course**

Ethylmalonic encephalopathy is a devastating, autosomal recessive metabolic disorder affecting the brain, gastrointestinal tract, and peripheral vessels of infants. The metabolic disorder was originally described in a Mediterranean (Hoffmann et al 1990) and an Italian family (Burlina et al 1994). The patients presented with neonatal hypotonia followed by severe progressive neurologic deterioration, pyramidal dysfunction, intellectual disability, orthostatic acrocyanosis with distal swelling, chronic diarrhea, recurrent petechiae, and abnormalities on brain MRI. MRI images showed areas of increased signal in the cerebellar white matter, caudate and lenticular nuclei. Some patients had an increased lactate resonance intensity in proton MR spectroscopy in the basal ganglia of both hemispheres, indicating an abnormality in oxidative metabolism (Grosso et al 2004). More patients from Spain (Garcia-Silva et al 1997), Saudi Arabia (Ozand et al 1994), Egypt (Ozand et al 1994), and Canada (Nowaczyk et al 1998a), with individual variations, have been described.

The disease course is variable. The patient from Spain was a 20-month-old boy with encephalopathy, petechiae, chronic diarrhea, and acrocyanosis. The brain MRI of this patient demonstrated bilateral lesions in the lenticular and caudate nuclei, the periaqueductal region, subcortical areas, white matter, and brainstem (Garcia-Silva et al 1997). The 5 patients from Saudi Arabia had similar clinical features but did not have chronic diarrhea, and failure to thrive was not prominent (Ozand et al 1994). All of these patients had retinal lesions characterized by tortuous veins. Three of them died following the sudden appearance of severe lesions in the basal ganglia. In 1 patient, the CT changes in the brain were suggestive of infarction. The patients who died manifested pulmonary congestion or edema and secondary respiratory difficulties during the terminal stage of the disease. All patients had mild-to-moderate hematuria, and 1 had a mild hemoperitoneum at the terminal stage. Nowaczyk and colleagues reported 2 siblings with ethylmalonic encephalopathy and malformations of the CNS (1 with tethered cord and the other with cerebellar tonsillar ectopia or Chiari I malformation) (Nowaczyk et al 1998a). Of 3 siblings in an American Hispanic family, a girl with ethylmalonic encephalopathy had dysmorphic features and hepatomegaly in addition to the described clinical features of this disease (Chen et al 1994).

In some patients atypical presentation has been reported. Heberle and colleagues reported a patient with the typical clinical picture and biochemical abnormalities, but, in addition, he presented with microcephaly, mild hepatomegaly, small penis, undescended testes, and horizontal nystagmus (Heberle et al 2006). Brain MRI revealed multiple areas of low and high signals in the basal ganglia and prominent frontal and temporal subarachnoid spaces. A new homozygous mutation in exon 3 of the ETHE1 gene was found.

Another child with ethylmalonic encephalopathy due to a homozygous mutation in the ETHE1 gene (R163W) presented atypically. No pathologic excretion of ethylmalonic acid was found, and the clinical picture was suggestive of a connective tissue disorder (vascular fragility, joint hyperlaxity, delayed motor development, and normal cognitive development). This case suggests that ethylmalonic aciduria is not a constant biochemical marker of this disease and that normal excretion of this metabolite, at least between metabolic decompensations, does not exclude this metabolic disorder.

Ethylmalonic encephalopathy may also masquerade as a hematological disorder with leukocytosis and thrombocytosis (Pavlou et al 2013) or fatal progressive pancytopenia (Hoffmann et al 1990) and may be associated with a rapidly progressive glomerulonephritis (Dweikat et al 2012). Early onset epilepsy presenting with West syndrome has been reported in 1 patient by Papetti and colleagues (Papetti et al 2015). Taken together, the clinical course of ethylmalonic encephalopathy is characterized by clinical heterogeneity, and Pigeon and colleagues report different clinical courses even in monochorionic twins (Pigeon et al 2009).

Few symptomatic patients with short-chain acyl-CoA dehydrogenase deficiency have been described, and it remains a
poorly defined entity. Two different clinical phenotypes have been delineated.

The first phenotype occurs in infants and small children. These patients can show a variable, often progressive presentation, including metabolic acidosis, failure to thrive, developmental delay, seizures, hypotonia, and myopathy. The second phenotype of SCAD deficiency occurs in middle-aged patients suffering from chronic myopathy (adult-onset) (Turnbull et al 1984).

A novel phenotype of multicore myopathy and ophthalmoplegia was described by Tein and colleagues (Tein et al 1999). The patient, a 13-year-old Israeli girl in whom there was no detectable SCAD protein on Western blot analysis, presented with congenital-onset facial and neck weakness, slowly progressive severe limb girdle and axial myopathy, respiratory weakness, cardiomyopathy, progressive joint contractures, lumbar lordosis, progressive external ophthalmoplegia with ptosis, and cataracts.

**Clinical symptoms that may be suspicious for SCAD-deficiency.** In contrast to other fatty acid oxidation disorders, fasting intolerance and/or hypoglycemia is not a prominent feature. Van Maldegem and colleagues report 3 individuals with SCAD deficiency who presented with hypoglycemia during fasting, but they conclude that SCAD deficiency may be diagnosed coincidently during metabolic work-up of hypoglycemia (van Maldegem et al 2010a).

Seidel and colleagues reported a 12-year-old boy who suffered from recurrent attacks of vomiting once or twice a year from infancy (Seidel et al 2003). The patient had a normal development. In twin sisters with SCAD deficiency, 1 developed hypotonia and a decreased level of consciousness following an upper respiratory infection at 5 months; the other remained asymptomatic (Ribes et al 1998).

Kurian and colleagues described for the first time 2 unusual cases of axonal neuropathy associated with SCAD deficiency. These 2 unrelated infants presented with profound generalized weakness preferentially affecting the upper limbs, generalized peripheral hypotonia, and absent deep tendon reflexes (Kurian et al 2004). An 8-month-old girl with SCAD deficiency presented with significant hypotonia and weakness (Okuyaz et al 2008). Ethylmalonic acid was increased in urine, and a variant SCAD gene polymorphism was found. The authors stress that severe infantile hypotonia can also be the only manifestation of ethylmalonic aciduria spectrum disorders.

Kilbane and colleagues report a case of malignant hyperthermia-like syndrome associated with hyperglycemic hyperosmolar nonketotic syndrome and SCAD deficiency (Kilbane et al 2006). The occurrence of brain malformations, such as small midline frontal meningocele, abnormal cortical gyration, partial agenesis of the corpus callosum, combined with infantile spasms, has been described by Mikati and colleagues in a female patient with SCAD deficiency (Mikati et al 2007). Battisti and colleagues reported the case of a 23-year-old male patient who had short stature, intellectual disability, recurrent vomiting, fevers, and seizures since infancy (Battisti et al 2007).

The clinical impact of SCAD deficiency has been investigated in several studies. Waisbren and colleagues describe the medical and neurodevelopmental characteristics of 14 children with SCAD deficiency (Waisbren et al 2008). The authors suggest that SCAD deficiency may be benign, respectively a nondisease. The clinical symptoms ascribed to SCAD deficiency may be reflective of ascertainment bias, alternatively early identification and treatment may prevent complications that may have occurred due to interaction between genetic susceptibility and other genetic factors or environmental stressors. They conclude that there is no genotype-phenotype correlation for this disease. Thus, SCAD deficiency may be solely a biochemical phenotype without any clinical manifestations (van Maldegem et al 2011). An association of SCAD deficiency and epilepsy in the Netherlands could not be verified by the authors. Another study in California examined a large series of SCAD-deficient patients and provided evidence that SCAD deficiency diagnosed by newborn screening represents a benign condition (Gallant et al 2012). A follow-up study of 16 children with SCAD deficiency showed that the majority of these patients had normal growth and development (Pena et al 2012). Novel molecular analysis and in silico tools may help to characterize ACADS variants, identifying severe mutations that may be of clinical relevance and indicating which patients could benefit from a long-term follow-up (Tonin et al 2016).

**Genetics of SCAD deficiency.** In addition to severe mutations, several common polymorphisms in the SCAD gene, especially 625G/A and 511C->T, may cause variable SCAD deficiency depending on additional genetic or environmental factors. The combination of these complex factors may result in borderline to mild ethylmalonic aciduria. Again, the clinical significance is unknown.

The combination of asymptomatic newborns with common polymorphisms can cause much confusion in evaluating
and treating individuals with possible SCAD deficiency (Jethva et al 2008).

**Prognosis and complications**

Ethylmalonic encephalopathy is usually lethal in infancy or early childhood. In SCAD deficiency, a wide clinical heterogeneity exists, ranging from death in the neonatal period to asymptomatic patients. It is reassuring that some of the early-onset patients completely recovered and have ultimately had normal growth and development. Long-term outcome beyond adolescence is unknown, specifically for the development of potential muscle weakness. Except for the avoidance of fasting, there is no proven efficacy from the usual treatments for fatty acid oxidation disorders in SCAD deficiency. Like other fatty acid oxidation disorders, acute episodes may carry a risk of mortality or permanent brain damage. Many patients can be easily managed by avoidance of prolonged fasts, if necessary; these patients have an excellent long-term prognosis. Patients with skeletal-muscle weakness or hepatic dysfunction have a more guarded prognosis because they seem to have a more severe defect. Hyperammonemia, the high levels of toxic short-chain fatty acids and reduced levels of ketone bodies may all contribute to the encephalopathy that occurs during acute episodes of SCAD deficiency.

**Clinical vignette**

The authors report a baby girl with ethylmalonic encephalopathy who presented with fatal progressive pancytopenia and psychomotor retardation (Hoffmann et al 1990). The patient was symptomatic from birth, when hematomas and petechiae were noted. The hematological symptoms were followed by progressive psychomotor retardation. Irregular nystagmoid eye movements and convergent strabismus were present from birth. Until the age of 9 months the psychomotor and social development was otherwise unremarkable. From the age of 11 months there was a significant loss of gross motor abilities.

**Diagnostic tests.** Routine investigations showed a hemoglobin of 146 g/L and a severe thrombocytopenia (19 000/µl). In the course of disease all 3 hematopoietic lineages became involved, resulting in a progressive impairment of hematopoiesis. After the first year of life thrombocytes fell below 10 000/µl. Because of increasing urinary and intestinal bleedings the patient had to be substituted regularly. At 2 years of age severe pancytopenia had developed. Thereafter, the patient gradually developed a hypersensitivity against HLA identical thrombocytes.

The first urinary specimen for organic acid analysis was done at 4 months of age. Urinary organic acid analyses consistently showed a highly increased ethylmalonic acid of up to 113 mmol/mol creatinine (normal < 5) accompanied by a tenfold increase in the excretion of methylsuccinate up to 29 mmol/mol creatinine. There was no dicarboxylic aciduria. Ethylmalonic acid in plasma was quantified by stable isotope dilution GC-MS with selected ion monitoring and found to be elevated to 5.2 µmol/L (control mean 0.45 µmol/L). Complex 1 and 4 enzyme activities in fibroblasts were significantly reduced. In mitochondrial DNA smaller deletions or mutations could not be found.

A CT scan at the age of 11 months showed generalized atrophy. Muscular biopsy revealed a depletion of glycogen and on electron microscopy paracrystalline inclusion bodies.

**Management and course.** At the age of 20 months dietary therapy with a low fat diet enriched with carbohydrates and protein was attempted with no significant clinical or biochemical improvement. A therapeutical trial of carnitine and riboflavin supplementation was also ineffective. The patient finally died in a cardiovascular arrest secondary to severe anemia at the age of 27 months.

**Biological basis**

**Etiology and pathogenesis**

Ethylmalonic encephalopathy is a devastating, infantile, autosomal recessive, metabolic disorder caused by defects in the mitochondrial sulfur dioxygenase, ETHE1.

**Biochemistry.** To investigate if the underlying biochemical consequences in ethylmalonic encephalopathy arise pathogenetically from an abnormal isoleucine metabolism, Nowaczyk and colleagues determined the response to oral L-isoleucine load (150 mg/kg) in a 5-year-old girl with this disease and in 3 healthy controls (Nowaczyk et al 1998b). Following the isoleucine load in the patient, there was an accumulation of 2-methylbutyrylglycine and a delayed and lower peak urinary excretion of tiglylglycine, suggesting a partial defect in 2-methyl-branched-chain acyl-CoA
dehydrogenase. In vitro determination of enzyme activity in cultured skin fibroblasts from patients with ethylmalonic encephalopathy was normal. The authors conclude that isoleucine is a source for the elevated ethylmalonic and methylsuccinic acids in affected patients. They suggest a functional, possibly secondary, deficiency of 2-methyl-branched-chain acyl-CoA dehydrogenase activity in vivo. McGowan and colleagues determined the influence of candidate amino acids (isoleucine and methionine) on the excretion of urinary ethylmalonic acid in patients with ethylmalonic aciduria (McGowan et al 2004). Loading with methionine increased the excretion of ethylmalonic acid, whereas loading with isoleucine did not. Restriction of the dietary intake of methionine decreased ethylmalonic acid excretion. The authors conclude that methionine is a precursor of ethylmalonic acid in ethylmalonic encephalopathy. How these findings can be related to the function of the defective gene remains to be determined.

**Genetics.** Until now 27 different mutations in the ETHE1 gene causing ethylmalonic encephalopathy have been identified (Tiranti and Zeviani 2013). Most of these cause loss of function through a premature stop codon, a frame shift mutation, or aberrant splicing; others are entire gene deletions and missense mutations in highly conserved portions.

**Pathophysiology.** Tiranti and colleagues identified the ETHE1 gene (MIM 608451) as containing the pathologic mutations in ethylmalonic encephalopathy (Tiranti et al 2004). The authors demonstrated that the D83198 protein product is targeted to mitochondria and internalized into the matrix after energy-dependent cleavage of a short leader peptide. The protein is required for metabolic homeostasis and energy metabolism. They discovered that ETHE1 protein works as a supramolecular, presumably homodimeric complex. A 3-dimensional model of the protein suggested that it is likely to be a mitochondrial matrix thioesterase acting on a still unknown substrate. Finally, they ruled out a pathogenic role of the 625G/A single nucleotide polymorphism in the SCAD gene in ethylmalonic encephalopathy.

Tiranti and colleagues created a ETHE1(-/-) mouse that showed the cardinal features of ethylmalonic encephalopathy (Tiranti et al 2009). They found high thiosulfate and sulfide concentrations in ETHE1(-/-) mouse tissues. Sulfide is a powerful inhibitor of COX and short-chain fatty acid oxidation, with vasoactive and vasotoxic effects that may explain the microangiopathy in ethylmalonic encephalopathy. Sulfide is detoxified by a mitochondrial pathway that includes a sulfur dioxygenase. Sulfur dioxygenase activity was absent in ETHE1(-/-) mice, whereas it was markedly increased by ETHE1 overexpression in HeLa cells and Escherichia coli. The authors concluded that ETHE1 is a mitochondrial sulfur dioxygenase involved in catabolism of sulfide that accumulates to toxic levels in ethylmalonic encephalopathy. Because the crystal structure of ETHE1 has been identified by Pettinati and colleagues (Pettinati et al 2015), further functional and mechanistic studies on ETHE1 can be done in the future. ETHE1 deficiency seems to influence several important cellular functions, such as enzyme function and gene expression, as it has been demonstrated by quantitative proteomics (Sahebekhtiari et al 2016).

The physiological role and pathogenic effects of sulfide focusing on ethylmalonic encephalopathy has been summarized and discussed by Tiranti and Di Meo (Tiranti and Zeviani 2013; Di Meo et al 2015).

**Bioenergetics.** Sulfide induces COX deficiency by heme A inhibition and accelerated long-term degradation of COX subunits (Di Meo et al 2011). Di Meo and colleagues conclude that the devastating effects of sulfide accumulation in ethylmalonic encephalopathy cannot be fully explained solely by COX deficiency in critical tissues, but are likely secondary to several toxic effects on a number of enzymatic activities in different tissues leading to multiorgan failure. Pathological hallmarks in an affected patient as well as in ETHE1(-/-) mice were COX-depleted cells and widespread endothelial lesions of arterioles, capillaries of the brain, and the gastrointestinal tract (Giordano et al 2012). Di Meo and colleagues observed that AAV2/8-mediated, ETHE1-gene transfer to the liver of a ETHE1(-/-) mouse model resulted in full restoration of sulfur dioxygenase activity, correction of plasma thiosulfate, a biomarker reflecting the accumulation of hydrogen sulfide, and clinical improvement (Di Meo et al 2012). The involvement of sulfide in redox regulation and cytoskeleton dynamics has been shown in an ETHE1(-/-) mouse model by Hildebrandt and colleagues (Hildebrandt et al 2013). The authors hypothesized that sulfide signalling specifically regulates mitochondrial catabolism of fatty acids and branched-chain amino acids.

After identifying the disease-causing gene of ethylmalonic encephalopathy (Tiranti et al 2004), Tiranti and colleagues hypothesized that the severe consequences of the malfunctioning of this protein may indicate an important role of the ETHE1 gene product in mitochondrial energy metabolism and homeostasis. This notion of an impaired mitochondrial energy metabolism is further supported by the fact that in several affected patients a selective vulnerability of the basal ganglia with atrophy and infarction on conventional MRI brain scans has been described (Grosso et al 2004).
SCAD deficiency is a defect in the mitochondrial beta-oxidation pathway and is caused by a deficiency of the first enzyme of the intramitochondrial beta-oxidation spiral called short-chain acyl-CoA dehydrogenase.

**Biochemistry.** Defective short-chain acyl-CoA dehydrogenation results in accumulation of butyryl-CoA, which is then carboxylated by propionyl-CoA carboxylase to form ethylmalonyl-CoA. This metabolite is either hydrolyzed to ethylmalonic acid or converted to methylsuccinyl-CoA by methylmalonyl-CoA mutase, yielding methylsuccinic acid on hydrolysis.

**Genetics.** At least 35 inactivating mutations and 2 polymorphic variants have been reported in the SCAD gene (Jethva et al 2008).

The variant allele (625A) was found in homozygous form in 60% of 135 patients with elevated ethylmalonic acid excretion compared to 7% of individuals in the general population (Corydon et al 1996). The authors suggested that the 625A variant allele is a susceptibility allele of the SCAD gene, which causes variable elevation of ethylmalonic acid in the urine and in combination with other genetic or environmental factors may lead to a functional impairment of the enzyme's catalytic activity. Subsequently, another possibly disease-associated susceptibility polymorphisms (511C>T) have been reported (Gregersen et al 1998). However, the 511T allele was found in 9.2% of 98 control individuals and in 5.6% of 266 patients with elevated ethylmalonic acid excretion according to Gregersen and colleagues (Gregersen et al 1998). Several novel mutations of SCAD deficiency (p.L93I, p.E228K, p.P377L, and p.R386H) have been identified in Korean patients (Kim et al 2016).

SCAD deficiency may be divided into at least 2 separate clinical and genetic phenotypes. One group is comprised of patients with conventional SCAD deficiency caused by disruptive mutations in the SCAD gene, and the second group consists of patients with a polygenic or multifactorial condition caused by the presence of a number of susceptibility alleles, located either in the SCAD locus, as is the 625A or 511T allele, or elsewhere, that may cause SCAD deficiency depending on the synergistic effect of additional genetic factors or cellular conditions. The different temperature profiles of the variant enzymes R147W (511T) and G185S(625A) in comparison to normal enzymes raised the notion that a decreased stability of the tetrameric structure or an instability to intermediates of the folding pathway of the protein may be responsible for reduced enzymatic activity in these patients (Gregersen et al 1998).

**Pathophysiology.** Acyl-CoA dehydrogenase deficiencies constitute an important group of inborn errors of metabolism. A reduced or absent enzymatic activity of short-chain acyl-CoA dehydrogenase (SCAD, EC 1.3.99.2), the first enzyme of the intramitochondrial short-chain beta-oxidation spiral catalyzing the dehydrogenation of short-chain fatty acids (C4-C6), is the cause of SCAD deficiency. Like the other 4 enzymes belonging to the acyl-CoA dehydrogenase gene family, SCAD is a homotetrameric mitochondrial flavoenzyme.

Wood and colleagues discovered a subline of BALB/c mice (BALB/cByJ) that excreted abnormally high concentrations of ethylmalonate, methylsuccinate, n-butyrylglycine, and n-butyrylcarnitine (Wood et al 1989). These metabolites suggested a defect in short-chain acyl-CoA dehydrogenase. Amendt and colleagues, who authenticated the SCAD deficiency of the BALB/cByJ mouse as a model of human SCAD deficiency, reported that SCAD-deficient mice and affected humans share similar clinical characteristics, including a tendency toward hypoglycemia, hepatic lipid deposition, and similar organic acidurias (Amendt et al 1992). In contrast to humans, the SCAD-deficient mice excreted large amounts of n-butyrylglycine and n-butyrylcarnitine, probably resulting from differences between rodents and humans in glycine conjugation of various acyl-CoA derivatives, particularly butyryl-CoA. As the BALB/cByJ mice had a lack of SCAD activity in all investigated tissues (liver, muscle, fibroblasts), Schuck and colleagues reported that in the rat cerebral cortex, ethylmalonic acid increases lipoperoxidation and protein oxidative damage and decreases nonenzymatic antioxidant defenses (Schuck et al 2010). The authors postulated that oxidative stress may be involved in the neuropathogenesis of ethylmalonic acidurias. Vulnerability to oxidative stress in SCAD-deficient fibroblast cultures is exacerbated by hyperthermia and can be rescued by antioxidants and bezafibrate (Zolkipli et al 2011). The authors suggested that an impairment of mitochondrial energy metabolism in muscle contributes to the pathogenesis of hypotonia, myopathy, and lactic acidosis in affected patients. In contrast, in vivo administration of ethylmalonic acid to young rats has no effect on mitochondrial energy metabolism (Ferreira et al 2006). The administration of a short-term high fat diet in ACADs-/- knock-out mice results in perturbation of mitochondrial energy metabolism (Ghosh et al 2016).

Beattie and colleagues reported biochemical correction of SCAD deficiency in the SCAD-deficient (BALB/cByJ) mouse after injection of recombinant adeno-associated viral vectors expressing mouse short-chain acyl-CoA dehydrogenase
(mSCAD) in the portal vein of these animals (Beattie et al. 2008).

Because SCAD deficiency does not impair long-chain fatty acid oxidation, it is unlikely that a defect in SCAD would have a major effect on the yield of energy from fatty acid oxidation. This notion is supported by the finding that SCAD-deficient patients are capable of mounting a ketogenic response. The fact that patients display such different clinical symptoms further indicates that the pathophysiology involves more than a simple energy deficit. Shirao and colleagues suggest the induction of mitochondrial fragmentation and autophagy by a mutant SCAD protein as possible pathophysiologic mechanisms in SCAD deficiency (Shirao et al. 2010). Furthermore, misfolded mutant SCAD protein elicits a toxic reaction in mitochondria, including mitochondrial fission and the production of oxidative stress in transiently transfected astrocytes (Schmidt et al. 2010). An alteration of mitochondrial proteins and a relation to mitochondrial dysfunction has been identified by proteomic studies in cultured human skin fibroblasts (Edhager et al. 2014) and in the mouse model of SCAD deficiency (Wang et al. 2014).

**Epidemiology**

Since the initial report, only about 40 cases of ethylmalonic encephalopathy have been described worldwide, suggesting that this condition is an ultra-rare autosomal recessive disorder. Most patients with ethylmalonic encephalopathy have been, with a few exceptions (Yoon et al. 2001), of Mediterranean (Hoffmann et al. 1990; Burlina et al. 1994; Garavaglia et al. 1994; Garcia-Silva et al. 1997; Grosso et al. 2002) or Arabic (Ozand et al. 1994) descent. However, the actual incidence of this condition could have been significantly underestimated because the biochemical phenotype may be incorrectly attributed to other metabolic disorders, particularly defects of the mitochondrial electron-transfer flavoprotein pathway. Several cases of ethylmalonic aciduria were initially diagnosed as glutaric aciduria type II, but this diagnosis was not confirmed by in vitro enzyme assays or molecular studies. Some of these cases could have been ethylmalonic encephalopathy.

The frequency of SCAD deficiency is unknown, but results from newborn screening suggest frequencies varying between 1:33,000 and 1:340,000 (Waisbren et al. 2008; Lindner et al. 2010).

**Prevention**

Because an effective treatment for ethylmalonic encephalopathy is not known, prevention of the disease is not possible. But genetic counseling or even prenatal diagnostics should be done when a disease-causing mutation could be identified in a family.

Prevention of metabolic decompensation in fatty acid oxidation disorders like SCAD deficiency consists of avoiding prolonged fasting periods, a continuous dietary treatment, and management of intercurrent illness. Fasting periods should be limited to 12 hours; during intercurrent illness, carbohydrate feeding should be provided every 4 to 6 hours. With gastroenteritis or the development of early signs of unusual lethargy, it is necessary to intervene promptly with intravenous glucose infusion. As many subjects with SCAD deficiency are completely asymptomatic, it is difficult to decide who might be a patient and would benefit from these measures.

**Differential diagnosis**

The differential diagnosis of persistent ethylmalonic aciduria includes not only ethylmalonic encephalopathy and SCAD deficiency but also the common SCAD variants: glutaric acidemia type II (sometimes described as ethylmalonic adipic aciduria), some forms of respiratory chain deficiencies, and Jamaican vomiting sickness. A diagnosis of ethylmalonic encephalopathy can be guided by rather specific clinical features like orthostatic acrocyanosis with distal swelling and recurrent petechiae. Clinically, ethylmalonic encephalopathy has some similarities with myo-, neuro-, gastrointestinal encephalopathy (MNGIE syndrome). Among 14 patients with Leigh syndrome and COX deficiency, 3 patients were reported to have chronic diarrhea (Van Coster et al. 1991). In a child with MELAS syndrome, purpura on the soles and palms and vascular changes with proliferation of abnormal mitochondria in cutaneous and muscular vessels have been reported (Fuji et al. 1991). Since 2004, the definitive diagnosis of ethylmalonic encephalopathy has become possible by mutation analysis.

The carnitine-deficient lipid storage myopathy in SCAD deficiency overlaps with MCAD deficiency and some clinical phenotypes of MADD. Other clinical features of this disease—metabolic acidosis, failure to thrive, developmental delay, seizures, and hypotonia (neonatal-onset)—show similarities to mitochondrial cytopathies. The typical clinical
presentation of fatty acid oxidation disorders with episodes of fasting-induced vomiting, lethargy, and coma with hypoketotic hypoglycemia is rarely seen in patients with SCAD deficiency. If these features are present, the following diseases must be considered in the differential diagnosis: plasma membrane carnitine transporter defect, carnitine palmitoyltransferase II deficiencies, acylcarnitine translocase deficiency, MCAD deficiency, very long-chain acyl-CoA dehydrogenase deficiency (VLCADD), long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD), trifunctional protein deficiency, 2,4-dienoyl-CoA-reductase deficiency, HMG synthase deficiency, HMG lyase deficiency, and glutaric aciduria type II. Other inborn errors of metabolism presenting with hypoglycemia and coma are organic acidurias (usually associated with more severe acidemia than fatty acid oxidation disorders) and disorders of galactose or fructose metabolism (galactosemia, hereditary fructose intolerance, fructose-1,6-bisphosphatase deficiency).

**Diagnostic workup**

The main biochemical features of ethylmalonic encephalopathy are increased urinary ethylmalonic and methylsuccinic acids associated with abnormal excretion of C4-C5 (n-butyryl-, isobutyryl-, isovaleryl-, and 2-methylbutyryl-) acylglycines and acylcarnitines and intermittent lactic acidosis. Urine organic acid analysis is performed by gas chromatography-mass spectrometry, the gold standard for identification of metabolic disorders from urine specimens (Blau et al 2014) and stable isotope dilution techniques for quantification, if necessary. Short- and branched-chain acylcarnitines may also be elevated in dry blood spot, plasma, or whole blood samples (Schulze-Bergkamen et al 2005). Usually 2-ethylmalonic aciduria can be regarded as indicative of a defect in fatty acid oxidation, so fatty acid oxidation disorders should always be investigated. Because respiratory chain deficiencies are an important differential diagnosis, the enzyme activities in different tissues (skin fibroblasts or muscle) may be determined. For several affected patients, a partial COX deficiency has been described in muscle. To search for the main neuropathological features like symmetrical lesions in the deep gray matter structures, an MRI scan of the brain is informative. Mutation analysis of the ETHE1 gene in available tissues will provide the definitive diagnosis.

Initial laboratory studies in the investigation of ethylmalonic aciduria should include blood glucose, lactate, ammonium, electrolytes, blood gases, a complete blood count, blood acylcarnitine profile, and quantitative urinary organic acid analysis by gas chromatography-mass spectrometry. Indicators for a defective SCAD activity may be acidosis, an increased anion gap, elevated blood urea nitrogen, ammonium and liver transaminases, and abnormal coagulation tests. Plasma carnitine levels, which can be normal or low, may be determined to exclude secondary (or primary) carnitine deficiency. The main feature of fatty acid oxidation disorders, hypoketotic hypoglycemia, is usually not present in SCAD-deficient patients. The biochemical hallmark of SCAD deficiency is an increased urinary excretion of ethylmalonic acid, the carboxylation product of butyryl-CoA with normal to slightly elevated excretion of other dicarboxylic acids. Methylsuccinic acid, butyrylglycine, and butyrylcarnitine may also be elevated in the urine of patients with SCAD deficiency, although these metabolites are also excreted by patients with multiple acyl-CoA dehydrogenation defects and ethylmalonic encephalopathy. Plasma C4-carnitine may be moderately increased.

Because affected patients do not consistently excrete characteristic metabolites, the diagnosis of SCAD deficiency may be difficult. The abnormal metabolic pattern is often amplified during illness or metabolic stress. A persistent increase of plasma butyryl-/isobutyrylcarnitine with ethylmalonic aciduria can be due either to ethylmalonic encephalopathy or to short-chain acyl-CoA dehydrogenase deficiency. Consequently, further investigations are required to differentiate the underlying defect in the case of this abnormal metabolic pattern. Enzymatic or molecular studies are indispensable for obtaining a definitive diagnosis. For direct enzyme measurement or for probing the metabolic pathway in vitro by using radiolabeled (16-2H3-palmitate, [1-14C]butyrate) or unlabeled (palmitic/butyric acid) fatty acids for measurement of C4-acylcarnitine production (Okun et al 2002), a skin biopsy may be performed. SCAD activity can be measured in cultured fibroblasts, muscle, or liver using the electron-transfer flavoprotein-linked dye reduction assay with immunoinactivation of the MCAD activity to confirm the diagnosis. Complete absence of activity toward butyryl-CoA in cultured fibroblasts, after incubation with an anti-MCAD antibody, proves SCAD deficiency. Immunoblot or electrophoretic analysis of the SCAD protein in different tissues (skin fibroblasts, liver, and muscle) may be performed to verify the diagnosis.

Mutation analysis of the 2 most common mutations (C511T and G625A), both conferring susceptibility to ethylmalonic aciduria, as well as mutation analysis of the whole gene may be investigated in DNA obtained from fibroblasts and leukocytes (Blau et al 2014). SCAD is known to be labile and easily affected secondarily. Because some patients thought to have SCAD deficiency due to increased ethylmalonate excretion also may have persistent elevation of lactate, the possibility of a primary lesion in the respiratory chain should also be considered.
Management

**Ethylmalonic encephalopathy.** No effective treatment for ethylmalonic encephalopathy is known.

**Treatment with cofactors and vitamins.** Riboflavin, carnitine, ascorbic acid, vitamin E, and glycine supplementation have been tried without benefit (Ozand et al 1994; Roe and Ding 2001). In contrast to these reports, some clinical studies report a benefit from riboflavin or coenzyme Q10 treatment in these patients (Yoon et al 2001; Yis et al 2015).

**Medical treatment.** Ozand and colleagues report a patient with ethylmalonic encephalopathy who remained stable on prolonged doses of methylprednisolone (Ozand et al 1994). The combined treatment with oral metronidazole and N-acetylcysteine has been reported to have some effect in these patients by Viscomi and colleagues (Viscomi et al 2010). N-acetylcysteine may also be given intravenously (Kiliç et al 2017).

**Dietary treatment.** Dietary therapies, such as a diet low in branched-chain or sulphur-containing (methionine) amino acids, have not been shown to be beneficial and are potentially harmful because of inducing malnutrition and metabolic imbalance.

**Treatment on the horizon.** In the mouse model an AAV2/8-mediated liver gene therapy has been established for ethylmalonic encephalopathy, but it has not yet been tested in patients (Di Meo et al 2012; Di Meo et al 2015). Dionisi-Vici and colleagues presented a report of an infant with ethylmalonic encephalopathy who received living-donor liver transplantation (Dionisi-Vici et al 2016). Neurologic improvement and reversal of biochemical abnormalities several months after the surgical intervention may indicate liver transplantation as an alternative therapeutic option in affected patients.

**SCAD deficiency.**

**Dietary treatment.** The management of SCAD deficiency, if at all necessary, is similar to the management of the other fatty acid oxidation disorders, including avoiding fasting by frequent feeding in order to prevent the use of fatty acids as a fuel, maintaining high carbohydrate and low fat intake, and treating intercurrent episodes of illness with intravenous glucose. In such a diet it is usually recommended that 70% to 75% of total energy intake is from carbohydrates (Blau et al 2014). A fat-restricted diet may put patients at risk of essential fatty acids deficiency; therefore, supplementation with essential fatty acids can be necessary in order to meet the requirements for age (1% to 4% of energy intake). The goal is to provide sufficient glucose to stimulate insulin secretion to levels that will suppress fatty acid oxidation in liver and muscle and will block adipose-tissue lipolysis. Many patients are able to tolerate fasting periods up to 12 hours. Determination of an individually safe fasting-tolerance should be done under controlled circumstances and careful clinical supervision and should include the determination of the plasma acylcarnitine profile and urinary organic acids at short intervals (Hoffmann et al 2017).

**Treatment with vitamins and carnitine.** Some patients with mild variants of MADD and SCAD deficiencies have been reported to respond to supplementation with high doses of riboflavin (100 to 300 mg per day), the cofactor for these enzymes (van Maldegem et al 2010b). Riboflavin supplementation (100 to 300 mg per day) in 3 divided doses should be systematically tested in all patients. However, some authors reported unsuccessful trials of riboflavin in patients with SCAD deficiency (Dawson et al 1995). In SCAD deficiency, carnitine levels can be very low as the result of urinary acylcarnitine losses. In cases of low plasma free carnitine levels, an oral supplementation of carnitine (50 to 100 mg/kg per day) should be considered in order to prevent deficiency and to allow the detoxification process to continue (Blau et al 2014).

**Special considerations**

**Pregnancy**

Maternal illness of an SCAD-deficient fetus during pregnancy has been reported (Blau et al 2014). Bok and colleagues reported a mother of a patient with SCAD deficiency who developed a hemolysis-elevated liver enzyme-low platelet (HELLP) syndrome while pregnant with the affected child (Bok et al 2003). The patient was homozygous for the inactivating 1138C>T mutation. This is the first report that SCAD deficiency may be related to maternal HELLP syndrome, as it is reported for long-chain 3-hydroxyacyl-dehydrogenase (LCHAD) deficiency. Prenatal diagnosis can be
performed by reverse transcription polymerase chain reaction (RT-PCR) for ethylmalonic encephalopathy (Drousiotou et al 2011).

**Anesthesia**

In patients with fatty acid oxidation disorders, precautions should be taken before anesthesia to avoid perioperative prolonged fasting periods (Ames et al 2012; Hoffmann et al 2017). Intravenous glucose infusion (8 to 12 mg/kg per minute) should be given to prevent activation of fatty acid oxidation. Metabolic acidosis should be corrected. Ringer’s lactate should be avoided because of lactic acidosis. Drugs stimulating lipolysis and fatty acid oxidation, like epinephrine and other beta-agonists, theoretically might pose a hazard for patients with fatty acid oxidation disorders. Enflurane was reported to increase free fatty acids during perioperative stress caused by minor elective surgery (Kleemann et al 1986). Premedication with morphine, flunitrazepam, and promethazine had no effect on plasma concentrations of free fatty acids (Hofmann and Kleemann 1991). Propofol infusion syndrome, a rare but frequently fatal complication in critically children given long-term propofol infusions, results in an impaired fatty acid oxidation and an inhibition of the respiratory chain at several points (Wolf et al 2001). It should not be used.

Farag and colleagues reported the anesthetic management of ventricular septal defect in a child with multiple acyl-CoA dehydrogenase deficiency and reviewed the literature about anesthetic management of patients with mitochondrial diseases undergoing cardiopulmonary bypass (Farag et al 2002). The anesthetic management included avoidance of inhalation anesthetics, maintenance of blood sugar within the normal limits, and normothermia in order to avoid additional stress by hypothermia. The patient tolerated the procedure well and experienced a good recovery. The anesthesia was performed with ketamine and fentanyl. The relaxation was done with rocuronium, although muscle relaxants are often avoided in mitochondrial cytopathies due to reports of prolonged recovery time (Naguib et al 1996). A review of the literature showed that volatile anesthetics have been used uneventfully in several case reports (Lauwers et al 1994). However, in 1 case report, a malignant hyperthermia-type episode occurred when inhalation anesthetics and succinylcholine were used (Ohtani et al 1985). Vigilant monitoring of respiratory function should be maintained because several authors report a decreased ventilatory response to hypoxia and hypercarbia in patients with mitochondrial cytopathies (Kitoh et al 1995). Turpin and colleagues report the anesthetic care of a child with SCAD deficiency and Chiari type I malformation presenting for posterior fossa decompression. The authors conclude that of primary importance to the anesthesiologist for the perioperative management of these patients are the possibilities of metabolic disturbance including hypoglycemia and metabolic acidosis, hypotonia with the potential for respiratory involvement, and central nervous system involvement including seizure disorder, airway management issues, and risk of hypoglycemia with prolonged fasting. They postulate that a screening for fatty acid oxidation disorders including SCAD deficiency should be considered in patients who develop unexplained problems such as acidosis or hypoglycemia during the perioperative period (Turpin and Tobias 2005).

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

**ICD and OMIM codes**

**ICD codes**

ICD-9:
Other and unspecified hyperlipidemia: 272.4
Other deficiencies of circulating enzymes: 277.6

ICD-10:
Disorders of fatty-acid metabolism: E71.3
Disorders of plasma-protein metabolism not elsewhere classified: E88.0

**OMIM numbers**

Ethylmalonic encephalopathy: #602473
Short-chain acyl-CoA (butyryl-CoA) dehydrogenase deficiency: #201470

**Profile**

**Age range of presentation**

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years

**Sex preponderance**

male=female

**Family history**

family history may be obtained

**Heredity**

autosomal recessive

**Population groups selectively affected**

Mediterranean and Arabic for ethylmalonic encephalopathy, but occurs worldwide
none selectively affected for SCAD deficiency

**Occupation groups selectively affected**

none selectively affected

**Differential diagnosis list**

cytochrome C oxidase deficiency (COX deficiency)
genetic defects in the fatty oxidation pathway
medium-chain acyl-CoA dehydrogenase deficiency (MCADD)
very-long-chain acyl-CoA dehydrogenase deficiency (VLCADD)
long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHADD)
mitochondrial cytopathies
primary respiratory chain disorders
Jamaican vomiting sickness
myo-neuro-gastrointestinal encephalopathy (MNGIE syndrome)
riboflavin-responsive multiple-chain acyl-CoA dehydrogenase deficiency
plasma membrane carnitine transporter defect (CTD)
carnitine palmitoyltransferase I/II deficiency (CPT I/II)
acylcarnitine translocase deficiency (Trans)
medium-chain acyl-CoA dehydrogenase deficiency (MCADD)
2,4-dienoyl-CoA-reductase deficiency (DER)
HMG synthase deficiency
HMG lyase deficiency
organic aciduria
multicore myopathy and ophthalmoplegia
malignant hyperthermia-like syndrome
metabolic myopathies
glycogen storage disorders
gluconeogenic defects
disorders of galactose or fructose metabolism
Reye syndrome
sudden infant death syndrome
hyperinsulinism
hypopituitarism

**Associated disorders**

fatty acid oxidation disorder
medium-chain acyl-CoA dehydrogenase deficiency
metabolic acidosis
orthostatic acrocyanosis

**Other topics to consider**

Glutaric aciduria
Long-chain fatty acid oxidation defects
Medium-chain acyl-CoA dehydrogenase deficiency
Multiple acyl-CoA dehydrogenase deficiency
Myoglobinuria
Primary carnitine transporter deficiency