Review

Inborn Errors of Ketone Body Metabolism and Transport: An Update for the Clinic and for Clinical Laboratories

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Abstract

Major progress occurred in understanding inborn errors of ketone body transport and metabolism between the International Congresses on Inborn Errors of Metabolism in Barcelona (2013) and Rio de Janeiro (2017). These conditions impair either ketogenesis (presenting as episodes of hypoketotic hypoglycemia) or ketolysis (presenting as ketoacidotic episodes); for both groups, immediate intravenous glucose administration is the most critical and (mHGGCS, *HMGCS2*) effective treatment measure. **Ketogenesis Deficiencies:** New biomarkers were described for mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (mHGGCS, *HMGCS2*) deficiency. New patient series refined clinical knowledge of 3-hydroxy-3-methylglutaryl-CoA lyase (HGGCL, *HMGCL*) deficiency. Although affected humans have not been described, two animal model phenotypes are pertinent: zebrafish deficient in monocarboxylate transporter 7 (MCT7, *slc16a6*) (decreased ketone body exit from hepatocytes) or mice lacking D-3-hydroxy-n-butyrate dehydrogenase (BDH1, *BDH1*) (isolated hyperacetoacetatemia; fatty liver). **Ketolysis Deficiencies:** Monocarboxylate transporter 1 (MCT1, *SLC16A1*) deficiency is a newly described defect of ketone body transport, joining deficiencies of succinyl-CoA:3-oxoacid CoA transferase (SCOT, *OXCT1*) and methylacetoacetyl-CoA thiolase (MAT, *ACAT1*). Some heterozygotes for MCT1 or SCOT deficiency develop ketoacidosis.

Keywords

acetoacetic acid, 3-hydroxy-*n*-butyric acid, acetone, ketogenesis, ketolysis, MCT, SLC, organic aciduria, leucine, isoleucine

Introduction

Ketone bodies are circulating metabolites that are primarily formed in the liver and play a key role in glucose-sparing energy supply. They are especially important for the brain, which is unable to take up and use fatty acids for energy. Ketone bodies originate from fatty acids and, to a lesser extent, from ketogenic amino acids such as leucine (Figure 1).[1-3] Ketone body synthesis (ketogenesis) first yields acetoacetic acid (AcAc) which is interconverted with D-3-hydroxy-*n*-butyric acid (3HB) in a reversible manner that reflects the redox state of the mitochondrial matrix. Acetoacetic acid can be decarboxylated (nonenzymatically) to acetone, which is not metabolized further. The term "ketone bodies" usually refers to this group of three compounds. D-3-hydroxy-*n*-butyric acid can then be transported out of the liver with the help of monocarboxylate transporter 7 (MCT-7; SLC16A6).[4] Ketone bodies are transported in the bloodstream and can enter extrahepatic cells via the MCT 1 (*SLC6A1* gene),[5] deficiency of which has recently been associated with

severe ketoacidosis.[6,7] In ketolysis (ketone body utilization), AcAc and 3HB (following oxidation to AcAc) are converted to acetyl-coenzyme A (acetyl-CoA).[1-3] A comprehensive overview of ketone body metabolism and its defects was published

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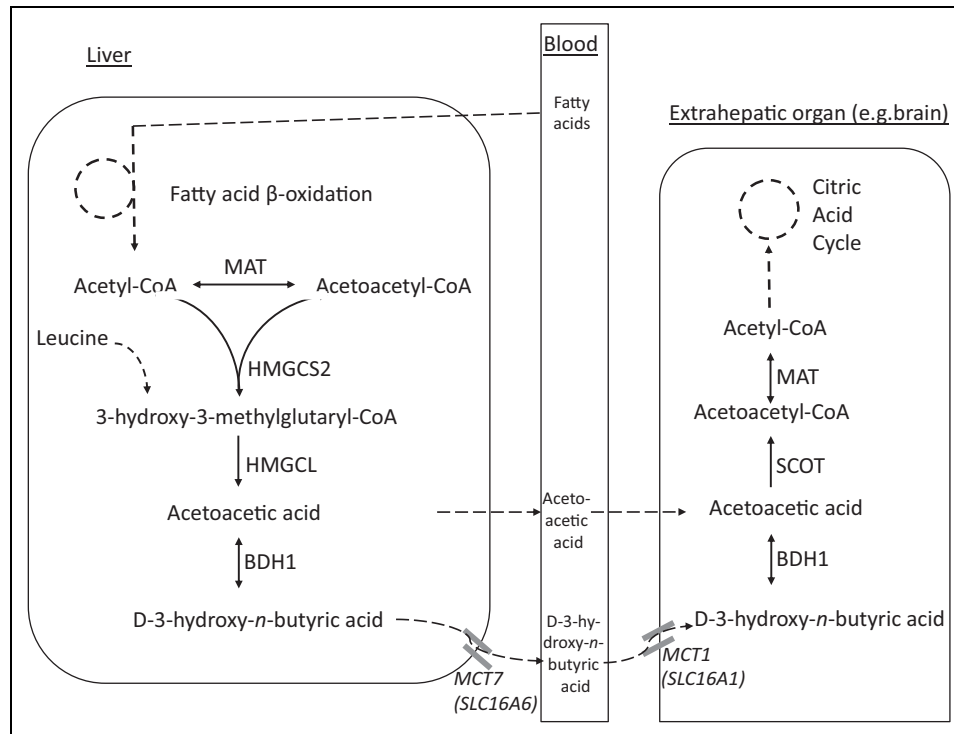Email: joern.oliver.sass@h-brs.de

Figure 1. Ketone body metabolism and transport. Schematic view of the enzymes and transporters of ketone body metabolism that are clearly linked to inborn errors. It is not exhaustive. In particular, additional monocarboxylate transporters (MCT) may be involved in ketone body transfer, and information is very limited regarding the transport of acetoacetic acid. Also, other sites than liver may provide small contributions to ketogenesis, for example, astrocytes and newborn gut. Mitochondrial acetoacetyl-CoA thiolase (MAT) and D-3-hydroxy-n-butyrate dehydrogenase (BDH1) participate in both ketogenesis and ketolysis. In liver mitochondria, during ketogenesis, MAT and other thiolases equilibrate the pools of acetoacetyl CoA (AcAc-CoA) and acetyl CoA (Ac-CoA). In contrast, in extrahepatic tissues, during ketolysis, MAT is the major mitochondrial thiolase that performs this reaction, and the most critical physiological role of MAT is in ketone body utilization. Note that up to now the purported role of MCT7 (encoded by *SLC*16A6) has been confirmed in the zebrafish only.

following the International Congress on Inborn Errors of Metabolism (ICIEM) in 2013.[8] Since then, important new developments have been reported in the field of ketone body metabolism and transport. Here, we describe clinically relevant features of ketone body physiology, then focus on developments since 2013.

Deficiencies of Ketogenesis

Clinical Context

The classic presentation of these disorders is episodic hypoketotic hypoglycemia, usually in infancy and usually in the context of fasting or reduced food intake. Hypoglycemia in association with hypoketonemia is a medical emergency because these patients lack both of the two major sources of energy for the brain, and permanent neurological damage may occur if the hypoglycemia is not corrected rapidly by glucose infusion. Hyperinsulinism and disorders of fatty acid oxidation are major differential diagnoses of hypoketotic hypoglycemia. Some other signs of the ketogenic defects are shown in Table 1.

Deficiency of Mitochondrial 3-Hydroxy-3-Methylglutaryl-CoA Synthase (MIM605911)

In ketogenesis, acetyl-CoA and acetoacetyl-CoA that result from fatty acid oxidation are converted to 3-hydroxy-3-methylglutaryl-CoA by mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (mHMGS; EC 4.1.3.5), encoded by *HMGCS2*. Deficiency of mHMGS commonly presents with episodes of (mostly hypoketotic) hypoglycemia, hepatomegaly, and acute encephalopathy. Of note, this clinical presentation closely resembles that of disorders of fatty acid oxidation. The pathogenesis of mHMGS deficiency is not completely resolved. Energy deficiency in extrahepatic tissues due to reduced ketone body supply is undoubtedly one element. The pathophysiology of this condition is not fully explained by energy depletion: A small group of mHMGS-deficient patients have become gravely ill during decompensations and have required dialysis.[9,10] We speculate that this may be due to increases in acetyl-CoA and acetoacetyl-CoA in liver mitochondria under conditions of ketogenic stress.[11]

Deficiency of mHMGS should be suspected in patients who clinically resemble the hepatic presentation of fatty acid oxidation disorders (episodes of hypoketotic hypoglycemia often

Table 1. Clinical Summary of known Disorders of Ketogenesis and Ketolysis in Humans.[a]

Protein	Gene	Confirmed Patients (Approximate no)	Cardinal Clinical Signs	Other Signs	Key Metabolites in Metabolic Decompensation
Ketogenesis disorders					
mHMGCS	*HMGCS2*	30	Hypoketotic hypoglycemia	Fatty liver	AC: acetylcarnitine (acylcarnitine C2) ↑ UOA: 4-hydroxy-6-methyl-2-pyrone + adipic acid ↑
HMGCL	*HMGCL*	200	Hypoketotic hypoglycemia	Fatty liver; Neurological dysfunction[b]; MRI findings in white matter (and basal ganglia)[c]; cardiomyopathy; pancreatitis (rare)	AC: acylcarnitines C5OH + C6DC ↑ UOA: 3-hydroxy-3-methylglutaric acid + 3-methylglutaric acid + 3-methylglutaconic acid + 3-methylcrotonylglycine ↑
Ketolysis disorders					
MCT1	*SLC16A1*	20	Ketoacidosis		UOA: acetoacetic acid and 3-hydroxy-*n*-butyric acid ↑
SCOT	*OXCT1*	30	Ketoacidosis		UOA: acetoacetic acid and 3-hydroxy-*n*-butyric acid ↑
MAT	*ACAT1*	250	Ketoacidosis	Neurological findings, including basal ganglion abnormalities	AC: acylcarnitines C5:1 + C5OH ↑ UOA: 3-hydroxy-2-methylbutyric acid + tiglylglycine + 2-methylacetoacetic acid[d] ↑

Abbreviations: AC, acylcarnitines; HMGCL, 3-hydroxy-3-methylglutaryl-CoA lyase; MAT, mitochondrial acetoacetyl-CoA thiolase; MRI, magnetic resonance imaging; UOA, urine organic acids.
[a]Disorders that also involve amino acid metabolism (deficiencies of HMGCL and MAT) affect a larger group of systems and have specific diagnostic metabolites.
[b]Some patients with HMGCL deficiency have a good neurological outcome but others have intellectual deficiency and/or other neurological sequelae. The neurological outcome is difficult to predict. Some but not all neurologically impaired patients have had prolonged symptomatic hypoglycemia.
[c]On cerebral MRI in HMGCL deficiency, T2-hyperintense foci are a diagnostic clue. They are found in the subcortical and periventricular white matter, they can coalesce, and regression of the lesions may occur. Basal ganglia may also be affected. The presence of lesions on MRI does not necessarily signal a worse clinical outcome. The MRI findings are noted here as a diagnostic aid, not as a prognostic indicator.
[d]If 2-methylacetoacetic acid is not detected in presence of elevated signals of, 3-hydroxy-2-methylbutyric acid and tiglylglycine, this can reflect the lability of this metabolite, but may also prompt consideration of the differential diagnosis HSD10 mitochondrial disease (MIM300438).

accompanying periods of fasting, hepatomegaly with possible cytolysis and steatosis). In contrast to fatty acid oxidation patients, mHMGS-deficient patients lack diagnostic circulating acylcarnitines.

Many have increased blood acetylcarnitine (C2 acylcarnitine), however, which if combined with nonspecific dicarboxylic aciduria strongly suggests mHMGS deficiency.[12] Specific biomarkers for mHMGS deficiency may have been found: Pitt et al reported seven novel organic acids in urine of patients with mHMGS deficiency during periods of metabolic decompensation.[10] This is potentially a diagnostic breakthrough; if confirmed in more patients, the pattern of 4-hydroxy-6-methyl-2-pyrone plus high concentrations of adipic acid in urine would be invaluable for specific diagnosis of mHMGS deficiency. Conboy et al obtained results resembling those reported by Pitt et al by retrospective analysis in another patient with genetically confirmed mHMGS deficiency but cast doubt on the diagnostic specificity of those biomarkers.[13] The stage is set to obtain answers about the specificity and sensitivity of these promising markers in the near future. Data obtained from urine of a single mHMGS-deficient patient investigated by comprehensive two-dimensional gas chromatography (GC) time-of-flight mass spectrometry suggested that crotonylglycine may be a diagnostic marker for mHMGS deficiency.[14] However, this also requires confirmation in more individuals with this disease.

Surprisingly, although mHMGS deficiency is a defect of ketogenesis, considerable ketonuria has been reported during metabolic decompensations of some patients. Possible sources of ketone bodies in mHMGS deficiency include extrahepatic pseudoketogenesis based on reversal of ketolysis[15,16] and ketogenesis via leucine and elevation of the L-enantiomer, L-3-hydroxy-*n*-butyric acid (formed as a thioester with CoA in the course of fatty acid oxidation), which is indistinguishable by conventional GC-mass spectrometry analysis of urinary organic acids from the D-enantiomer. The diagnosis of mHMGS deficiency is usually confirmed by mutation analysis. Enzyme activity testing would require liver tissue and could be subject to interference by cytoplasmic HMGS encoded by *HMGCS1*, which catalyzes the same reaction in the synthetic pathway of isoprenoids and cholesterol.

Deficiency of 3-Hydroxy-3-Methylglutaryl-CoA Lyase (MIM246450)

The cleavage of 3-hydroxy-3-methylglutaryl-CoA to acetyl-CoA and the ketone body acetoacetate is catalyzed by 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL; EC 4.1.3.4). In this condition, episodes of hypoglycemia and metabolic acidosis are important features. As in mHMGS deficiency, ketone body formation from fatty acids is impaired, but in contrast to mHMGS deficiency, leucine

degradation is also impaired. Because of this, laboratory diagnostics are usually straightforward in HMGCL deficiency, since characteristic metabolites derived from leucine degradation are continuously present in urinary organic acids (elevations of 3-hydroxy-3-methylglutaric, 3-methylglutaric, 3-methylglutaconic acids, and 3-methylcrotonylglycine). The blood acylcarnitine pattern is usually abnormal, showing elevated acylcarnitines C5OH and C6DC. Confirmatory testing can be done by enzyme assay in cultivated fibroblasts, native or immortalized lymphocytes, or by demonstrating the presence of pathogenic variants in the *HMGCL* gene with appropriate segregation in the family. A recent study on 37 patients from 13 metabolic centers revealed no obvious genotype–phenotype correlation.[17] All patients were symptomatic, mostly within the first year of life and with acute metabolic decompensation, about half of them during the very first days of life. While physical development was generally normal, long-term neurological complications were common. About 25% of patients showed severe mental impairment. Brain magnetic resonance imaging (MRI) was abnormal in 87% of the investigated patients, but in agreement with other studies, these MRI findings did not correlate with neurological symptoms.

Of technical note, it was recently demonstrated that following methylation for organic acid analysis in HMGCL deficiency, derivatized acetoacetate can be formed as a chemical artifact by the temperature-dependent degradation of derivatized 3-hydroxy-3-methylglutaric acid in the GC injector.[18]

Eight pregnancies in 5 women with HMGCL deficiency have been reported.[19-22] Five pregnancies resulted in the birth of a healthy child at term. Spontaneous abortion occurred in three pregnancies, and in one of these pregnancies, the mother died. Two of the three miscarriages occurred during severe metabolic decompensations. It is plausible that such severe metabolic stress would increase the risk of miscarriage. Notably, mouse fetuses with complete HMGCL deficiency die prior to birth.[23] Regarding maternal health, it is important to recall that pregnancy is a ketogenic state and that even during adult life, patients affected by disorders of ketogenesis such as HMGCL deficiency remain susceptible to decompensations that can be severe and even fatal.[1]

Deficiency of D-3-Hydroxy-n-Butyrate Dehydrogenase

Acetoacetic acid formed by ketogenesis can be reduced to 3HB, via a reversible reaction catalyzed by D-3-hydroxy-*n*-butyrate dehydrogenase (EC 1.1.1.30), encoded by *BDH1*.[24] BDH1 deficiency has not been reported in humans, but in mice, Otsuka et al engineered a *Bdh1* knockout model.[25] Affected mice survived without major problems and showed normal fertility. In contrast to wild-type mice, in which the major circulating ketone body during fasting is 3HB, BDH1-deficient mice demonstrate an increase in AcAc. Intriguingly, these mice also develop fatty liver, suggesting that the AcAc-3HB redox couple is important for maintaining normal liver energy homeostasis.

Deficiency of SLC16A6

In zebrafish, Hugo et al reported that *slc16a6a* (solute carrier family 16a, member 6a) encodes a transporter of 3HB required for hepatocyte secretion of ketone bodies during fasting.[4] Fish with a loss of function mutation in *slc16a6a* developed hepatic steatosis. Expression of a human *SLC16A6* transgene in these fish rescued the mutant phenotype. It is tempting to speculate that a comparable, mainly hepatic, presentation may occur in people who are deficient in the orthologous human gene *SLC16A6*, encoding MCT7, but to our knowledge, such individuals have not been reported.

Disorders of Ketolysis

Clinical Context

In these conditions, insufficient ketolysis can result in accumulation of ketone bodies with severe, potentially life-threatening episodes of ketoacidosis. Elevated ketone body levels occur normally with fasting, but in individuals with ketolysis defects, ketosis is much more severe than in normal controls. Other causes of enhanced ketogenesis include prolonged physical exercise that mobilizes fat stores, highly fat-enriched diet conditions (ketogenic diet), or any other condition in which carbohydrate-derived energy supply is reduced with activation of adipocyte lipolysis. The latter conditions are obvious from the clinical history and normally do not cause severe ketoacidotic episodes.

In nondiabetic individuals, the presence of repeated severe episodes of ketoacidosis, or the presence of ketonuria in patients who are not fasting, suggests one of these conditions. Because some degree of ketosis occurs normally during many pediatric infections and other stresses, clinical judgment is essential to decide whether the level of ketosis is disproportionately high, meriting further investigation. A low ratio of plasma-free fatty acids to plasma 3-hydroxybutyrate during a ketotic episode may be useful in distinguishing ketolytic deficiencies from the normal fasting response.[1,8] One of the inborn errors of ketolysis, 2-methylacetoacetyl-CoA thiolase (MAT) deficiency, has a diagnostic pattern of organic acids and acylcarnitines, but these findings can be subtle.[26]

Deficiency of MCT 1 (MIM616095; Mutations in SLC16A1)

In 2014, van Hasselt et al reported MCT1 deficiency as a novel genetic cause of massive ketoacidosis.[6] The MCT1, which is encoded by *SLC16A1*, transports a range of monocarboxylate metabolites including ketone bodies. Interestingly, van Hasselt et al demonstrated that clinical symptoms occurred not only in patients who were homozygous for *SLC16A1* deficiency but also in some heterozygous individuals with only a single mutation. This was confirmed by Balasubramaniam et al who have reported symptomatic half-brothers with the same mother but different fathers.[7] Both reports suggest that under some circumstances, heterozygous MCT1 deficiency can lead to ketoacidosis.

Succinyl-CoA: 3-Oxoacid CoA Transferase Deficiency (MIM245050; Mutations in OXCT1)

The first rate-limiting enzyme of ketolysis is succinyl-coenzyme A:3-oxoacid coenzyme A transferase (SCOT; EC 2.8.3.5) which activates AcAc to acetoacetyl-CoA. To undergo metabolism, 3HB must be oxidized to AcAc by BDH1 prior to activation by SCOT. Shafqat et al have determined the crystal structure of human SCOT, providing a molecular understanding of the mutations reported until 2013 based on their potential structural effects.[27]

Following the report by Merron and Akhtar,[28] in 2017 Sulaiman et al reported the successful management of a second case of pregnancy and delivery in a woman with SCOT deficiency.[22] This patient required multiple hospitalizations for intravenous glucose infusion due to ketoacidotic episodes, although she had dietary management during pregnancy. During labor and delivery, she was given epidural anesthesia to avoid physiological stress of pain and received adequate intravenous infusion and carnitine supplementation.

Cotter et al[29] showed that mice heterozygous for SCOT deficiency have significantly elevated levels of ketone bodies (particularly after fasting), and Sasai et al[30] have shown that humans who are heterozygous for OXCT1 mutations are also prone to the development of severe ketoacidosis.

Intriguingly, as in heterozygotes for MCT1 deficiency, additional factors appear to be required for ketoacidosis in heterozygotes for SCOT deficiency, because most heterozygotes do not experience such episodes. Presumably, under conditions of high ketone body flux, both alleles of SCOT and MCT1 are required to maintain normal plasma levels.

2-Methylacetoacetyl CoA Thiolase (Mitochondrial Acetoacetyl-CoA Thiolase T2, "Beta-Ketothiolase") Deficiency (OMIM203750; Mutations in ACAT1)

In 2017, large cohorts of patients with genetic deficiency of 2-methylacetoacetyl CoA thiolase (MATD) were reported. Importantly, MAT (EC 2.3.1.9) is not only involved in ketone body utilization but also catalyzes a step of isoleucine catabolism.[1,2,3]

Paquay et al reported 26 French patients with MATD who had been registered between 1986 and 2014. Although 61% of them required intensive care, most patients had a normal neurodevelopment, while 23% presented with neurological findings.[31] The study confirmed the—still unexplained—observation that neurological impairment (namely, with extrapyramidal signs) in MATD may occur in the absence of systemic ketoacidotic decompensations. The authors could not demonstrate a detectable effect of protein restriction on the prevention of neurological symptoms. This suggests that processes of brain metabolism that are not directly connected to protein intake may be responsible for the neurological decompensations that occur in some patients with MAT deficiency. This was discussed in a case report of such a patient, where it was hypothesized to arise from disequilibrium of acyl-coenzyme A pools in a cell-autonomous fashion[32] (discussed more fully by Mitchell et al).[11]

Of 41 patients with MATD born to nonconsanguineous parents in Vietnam between 2002 and 2016, 95% experienced episodes of ketoacidosis between the ages of 6 and 18 months.[33] There was a broad range in the age of onset, severity, and outcome of ketoacidotic episodes even among patients who shared the same ACAT1 genotype and also similar ancestry and living conditions. This study demonstrates the lack of genotype–phenotype correlations in MATD. Abdelkreem et al described 10 patients with MATD, of whom 8 were born in the city of Hyderabad (Telangana State, Southern India), suggesting that MATD may have a particularly high incidence there.[34] All 10 presented with ketoacidotic episodes, although of variable severity. Grünert et al reported 32 patients with MATD who were mainly of European/Turkish origin; 63% presented with an acute metabolic decompensation at a median age of 1 year.[35] Although fatal outcomes are documented in some patients with MATD, this study suggests that MATD may be a rather benign metabolic disorder, with a substantial fraction of asymptomatic individuals. Neither a benefit of protein restriction nor a genotype–phenotype correlation was obvious. Despite the important data contributed by these studies, many questions remain: the true impact of protein restriction and its relationship, if any, to systemic ketoacidotic episodes and to organ-specific neurological and other complications of MATD.

Deficiency of Cytosolic Acetoacetyl-CoA Thiolase (MIM614055)

In 2 girls described in 1977 and 1984 (respectively with developmental delay and metabolic reaction to a ketogenic diet and persistent ketonuria), evidence was presented in favor of a deficiency of cytosolic acetoacetyl-CoA thiolase (EC 2.3.1.9, gene ACAT2), which is part of cholesterol biosynthesis.[36,37] Although this hypothesis is intriguing, it is important to note that at the time of publication, optimized assays for this enzyme activity and molecular analysis of ACAT2 were not available. The clinical phenotype remains obscure, and the existence of cytosolic acetoacetyl-CoA thiolase deficiency still requires proof.

Treatment of Inborn Errors of Ketone Body Metabolism

Inherited disorders of both ketogenesis and ketolysis result from the stimulation of ketone body flux. The most important element in the treatment of both types of disorder is rapid intravenous glucose administration, which almost instantaneously stimulates insulin secretion, arresting adipocyte lipolysis, reducing the entry of fatty acids into mitochondria for beta oxidation, and suppressing mHMGS activity.[38] We do not recommend dietary fat restriction for these disorders, but very-high-fat (ketogenic) diets should be avoided. A benefit from carnitine supplementation is not proven, but it seems safe and reasonable to supplement, particularly if hypocarnitinemia is present.

Other treatment considerations for individual conditions are beyond the scope of this review but are considered elsewhere, including the special treatments that apply to the concurrent impairment of the degradation of amino acids, present in addition to ketone body metabolic deficiencies in HMGCLD and MATD.[1,2]

Conclusions

Between the 2 ICIEM conferences in 2013 and 2017, considerable progress was made, and the field of inborn errors of ketone body transport and metabolism has become dynamic. In disorders of ketogenesis, new biomarkers have been suggested for mHMGS deficiency. The largest study so far reported on the outcome in HMGCL deficiency appeared, showing early onset and a substantial fraction of patients with severe neurological outcomes.

MCT1 deficiency was discovered and shown to greatly reduce ketone body transport into cells. Monocarboxylate transporter 1 deficiency accounts for a substantial fraction of previously unexplained cases of severe recurrent ketoacidosis. In both MCT1 and SCOT deficiencies, symptomatic heterozygotes have been described. Although the majority of heterozygotes appear to be asymptomatic, these observations highlight an important role of additional genetic and/or environmental factors in triggering ketoacidotic crises. The striking phenotypes of zebrafish with mutations in the orthologous gene to human *SLC6A16*, encoding MCT7 (depression of 3HB exit from hepatocytes), and of mice deficient in BDH1 (hyperacetoacetatemia and fatty liver) may provide useful reference points in the future for the discovery of humans with these deficiencies.

Declaration of Conflicting Interests

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