CHAPTER 37

Fatty acid mitochondrial disorders

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Introduction

Lipid storage myopathies (LSMs) represent various disease entities whose biochemical defects are heterogeneous [1]; these disorders might be due either to defects of the carnitine membrane carrier or to enzymatic defects in beta-oxidation of long-chain fatty acid (LCFA). L-carnitine, carnitine palmitoyltransferase I (CPT I), carnitine acyltranslocase, and CPT II provide a mechanism whereby long-chain fatty acyl-CoA molecules are transferred from the cytosol across the outer and inner mitochondrial membrane to the mitochondrial matrix, where they undergo beta-oxidation [2]. A series of enzymes bound to the mitochondrial inner membrane or dissolved in the matrix transform fatty acyl-CoA into acetyl-CoA (figure 37.1). A mitochondrial trifunctional protein associated to the inner mitochondrial membrane has been identified that performs three different enzymatic activities during LCFA oxidation. The description of the disorders has been organized according to the pathway of LCFA transfer and oxidation.

Search strategy

The task force for metabolic disorders systematically searched the MEDLINE database using key words, and examined textbooks and existing guidelines. According to the guidance for the preparation of neurological management by European Federation of Neurological Societies task force [3], articles were included if they contained data that could be rated according to grades of recommendation for treatment classified in terms of evidence-based medicine. Most guideline recommendations in this document are derived from case reports (Class IV evidence), as no large trials have been conducted in fatty acid disorders. These guidelines reflect consensus in the opinions of experts in the field (Good Practice Points). The consensus was reached by analysing series of treated patients and discussing pre-existing guidelines.

Results

CPT II deficiency

In the most typical presentations, CPT II deficiency is seen in young adults (table 37.1) experiencing episodes of muscle pain and rhabdomyolysis triggered by prolonged exercise, fasting, cold, or a combination of these. The disease is autosomal recessive and is mostly seen in males, but intolerance to exercise might be observed also in carriers of CPT II mutations, suggesting a dominant negative effect of this tetrameric protein [4]. The rhabdomyolytic attacks are associated with pain, stiffness without cramps, and highly elevated creatine kinase levels (about 50,000 U or maybe even up to 200,000 U), reflecting muscle necrosis. This may lead to acute renal failure.
Neurological Problems

CPT II deficiency leads to an increase of serum palmitoylcarnitine (C16:0) and oleoylcarnitine (C18:1), whereas short- and medium-chain acylcarnitines are normal (figure 37.3), and in attacks free carnitine is low. Only a small amount of plasma (100 μl) or blood spotted onto filter paper (Guthrie card) is required. It is important to collect samples from patients when they are acutely ill, since a non-significant profile can be observed when patients are metabolically well equilibrated.

It is noteworthy that CPT II patients show the same elevated long-chain acyl-carnitine profile in plasma as carnitine/acylcarnitine translocase (CACT) deficiency. These disorders can easily be distinguished by their clinical presentation. However, the clinical presentation of the severe hepato-cardio-muscular form of CPT II deficiency can significantly overlap with that of CACT deficiency. In most cases, a direct measurement of enzymatic activity is required to differentiate between these two metabolic defects. Tandem mass spectrometry of serum acylcarnitines is a rapid screening test that should be included early in the diagnostic work-up of patients with recurrent myoglobinuria, recurrent muscular weakness, and myalgia.

**Table 37.1** Carnitine palmitoyltransferase (CPT) II deficiency.

<table>
<thead>
<tr>
<th>Young adults</th>
<th>Paroxysmal myoglobinuria</th>
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<tr>
<td>Residual: malonyl-CoA insensitive CPT activity</td>
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<tr>
<td>CPT gene is located in chromosome 1</td>
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<tr>
<td>Serine 113 to leucine is the most common missense mutation 6% cases (429C &gt; T)</td>
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**Diagnosis**

CPT II deficiency was routinely diagnosed by the determination of enzyme activity in muscle biopsies involving the time-dependent conversion of radiolabelled CPT II substrates by the isotope-exchange assay. Now, when available, the diagnosis can be made on the basis of genetic analysis (figure 37.2) and acylcarnitine profile.

Analysis of acylcarnitines in the blood, using tandem mass spectrometry, was developed in the late 1980s, allowing the diagnosis of most inborn errors of fatty acid metabolism, including CPT II defects. A characteristic profile of blood acylcarnitines has been reported [5]:

**Figure 37.1.** Pathway of long-chain fatty acid oxidation by enzymes in the inner mitochondrial membrane. CPT II, carnitine palmitoyltransferase II; VLCAD, very-long-chain acyl-CoA dehydrogenase; FAD, flavine adenine dinucleotide; FADH₂, reduced form of FAD; ETF, electron-transferring flavoprotein (RED, reduced; OX, oxidized); ETFDH, electron transfer flavoprotein dehydrogenase (RED, reduced; OX, oxidized); LCEH, long-chain enoyl hydratase; LCHAD, long-chain beta-hydroxy acyl-CoA-dehydrogenase; NAD, nicotinamide adenine dinucleotide (NADH₂, reduced form of NAD); LCKT, long-chain beta-keto thiolase; CAR, carnitine; CoA, coenzyme A. The other co-factors and enzymes are in either the cytosol or the mitochondrial matrix.

CPT II deficiency leads to an increase of serum palmitoylcarnitine (C16:0) and oleoylcarnitine (C18:1), whereas short- and medium-chain acylcarnitines are normal (figure 37.3), and in attacks free carnitine is low. Only a small amount of plasma (100μl) or blood spotted onto filter paper (Guthrie card) is required. It is important to collect samples from patients when they are acutely ill, since a non-significant profile can be observed when patients are metabolically well equilibrated.
The acylcarnitine profile has also demonstrated its high value as a fast and non-invasive method for the presymptomatic detection of inborn errors of fatty acid oxidation in newborn screening. Overnight fasting is useful but may lead also to unexpected hypoglycaemic episodes.

In general, patients with CPT II deficiency must avoid triggering factors of metabolic crisis such as fasting, cold, or prolonged exercise under fasting or stress-fuel conditions. However, a high-carbohydrate diet (20% fat, 15% protein, 65% carbohydrate) improves exercise tolerance, as indicated by a lowering of perceived exertion and an increased duration of exercise [7]. An anaplerotic diet using medium odd-chain triglycerides (triheptanoin) might improve cardiomyopathy, muscle weakness, and rhabdomyolysis. This kind of therapy is based on the concept that triheptanoin as an anaplerotic

**Figure 37.2.** Structural organization and mutational spectrum of the carnitine palmitoyltransferase II gene.

The acylcarnitine profile has also demonstrated its high value as a fast and non-invasive method for the presymptomatic detection of inborn errors of fatty acid oxidation in newborn screening. Overnight fasting is useful but may lead also to unexpected hypoglycaemic episodes.

### Recommendations

Preventing episodes of myoglobinuria is important, and this can be achieved by avoiding strenuous exercise during fasting or cold. During an attack, infusion of a 5% glucose solution is useful as an alternative metabolic fuel. According to published guidelines, a standard treatment protocol for myoglobinuria [6] is intravenous infusion of hypotonic sodium chloride and sodium bicarbonate (sodium chloride 110 mmol/l, sodium bicarbonate 40 mmol/l) in 5% glucose solution to which 10 g of mannitol per litre is added in a 20% solution. In a person weighing 75 kg, the solution should be infused at a rate of 12 l/day in order to obtain a diuresis of 8 l/day and keep the pH above 6.5. This therapeutic regimen will control both hyperkalaemia and acidosis, and therefore might prevent acute renal failure.

In general, patients with CPT II deficiency must avoid triggering factors of metabolic crisis such as fasting, cold, or prolonged exercise under fasting or stress-fuel conditions. However, a high-carbohydrate diet (20% fat, 15% protein, 65% carbohydrate) improves exercise tolerance, as indicated by a lowering of perceived exertion and an increased duration of exercise [7]. An anaplerotic diet using medium odd-chain triglycerides (triheptanoin) might improve cardiomyopathy, muscle weakness, and rhabdomyolysis. This kind of therapy is based on the concept that triheptanoin as an anaplerotic
compound provides an alternative substrate for both the tricarboxylic cycle and the electron transport chain, and may thus restore energy production [8–10]. A potential new therapy is being investigated using peroxisome proliferator-activated receptor (PPAR-delta) agonists, such as bezafibrate, which has the ability to partially or totally restore fatty acid oxidation in patients with the adult form of CPT II deficiency. A basic study [11] showed that bezafibrate treatment of mild-type CPT II-deficient fibroblasts resulted in a time- and dose-dependent increase in CPT II mRNA and residual enzyme activity, and led to a normalization of 3H-palmitate and 3H-Myristate cellular oxidation rates, suggesting that PPARs could be therapeutic targets for the correction of hereditary beta-oxidation defects. Bezafibrate did not correct fatty acid oxidation in fibroblasts from patients with a severe CPT II-deficient phenotype.

A French group [12] evaluated the efficacy of bezafibrate as a treatment in six adults with the mild adult form of CPT II deficiency. After bezafibrate treatment, the palmitoyl L-carnitine oxidation levels and the CPT II mRNA in skeletal muscle increased significantly, the episodes of rhabdomyolysis decreased, and the quality of life (evaluated with the use of the 36-Item Short-Form General Health Survey) improved considerably. The results of this pilot trial showed a therapeutic efficacy of bezafibrate, suggesting that further study of this agent for the pharmacological treatment of the mild form of CPT II deficiency might be of interest.

Bezafibrate has been prescribed for more than 25 years as a hypolipidaemic agent, in large cohorts of adults, and is generally considered to have a good safety profile. Occasionally, a drug-induced increase in plasma levels of creatine phosphokinase can be observed. However, bezafibrate-induced rhabdomyolysis is extremely rare and has only been reported in patients with renal insufficiency who tend to accumulate the drug.

Figure 37.3. Tandem mass acyl-carnitine spectra of serum of a normal subject (A) and a CPTII-deficient patient (B). In CPTII deficiency a characteristic elevation of palmitoyl-carnitine (C16) and oleoyl-carnitine (C18:1) can be observed. 227 Da: free carnitine, 263 Da: acetyl-carnitine, 291 Da: butyryl-carnitine, 311 Da: isovaleryl-carnitine, 347 Da: octanoyl-carnitine, 437 Da: myristoyl-carnitine, 459 Da: palmitoyl-carnitine. The peaks related to palmitoyl-carnitine and oleoyl-carnitine are enclosed in boxes.
Carnitine transport defects
Primary L-carnitine deficiency syndromes are rare biochemical disorders and can be classified on the basis of clinical and biochemical criteria into muscle carnitine deficiency and systemic carnitine deficiency. A carnitine deficiency syndrome should be suspected in a patient with LSM when the following symptoms are present: hypoglycaemia, with or without ketoacidosis with a Reye-like syndrome, myalgias, weakness, abnormal fatigability, and cardiomyopathy with left axis deviation [13, 14]. Primary systemic carnitine deficiency is a well-recognized treatable entity of childhood (table 37.2) characterized by progressive cardiomyopathy, LSM, attacks of hypoglycaemia, and hepatomegaly with a Reye-like syndrome that may lead to permanent brain damage [15].

Diagnosis
In several cases, a defect of the carnitine ‘high-affinity’ transport organic cation transporter 2 (OCTN2) gene has been demonstrated in cultured fibroblasts, and genomic DNA can be screened for mutations [16, 17].

Guidelines for therapy
Carnitine supplementation corrects cardiomyopathy and other clinical signs [13]. In some cases, this treatment may prevent the need for cardiac transplantation. The L-carnitine dose may vary from 100 to 600 mg/kg per day on the basis of the calculated carnitine depletion from muscle, liver, heart, and kidney. Individually adjusted dosing may require plasma level measurements. No side effects are noted for L-carnitine supplementation except occasional diarrhoea or a fishy body odour. In some cases, a medium-chain triglyceride diet may be added (Class IV evidence).

Muscle carnitine deficiency
In primary muscle carnitine deficiency, the clinical syndrome is confined to skeletal muscle [18, 19]; the clinical features are episodes of fluctuating muscle weakness, affecting mostly the limb and neck muscles, and severe myalgia.

Diagnostic guidelines and therapy
The patients show appropriate ketogenesis on fasting and on a fat-rich diet. Biochemical features are low muscle carnitine (below 15%) and absence of organic aciduria. Carnitine concentrations in the plasma and liver are normal. There is in vitro stimulation by L-carnitine of labelled palmitate and oleate oxidation. Although much is known about the mechanisms of carnitine transport, data on muscle-specific transport (low affinity) in human muscle carnitine deficiency cases are still scanty. In a childhood case, an abnormal low-affinity carnitine transport [19] was found in cultured muscle. This could be due to either a delayed maturation or an abnormal carnitine carrier protein. The available evidence indicates that the low muscle content is the result of a genetic defect in the sarcolemmal carnitine transporter. Therefore, muscle carnitine deficiency could be caused by an abnormal low-affinity carrier or by a low amount of sarcolemmal carnitine carriers. It is distinguished from carnitine insufficiency by the absence of acylcarnitine elevation in plasma or urine.

Treatment with an L-carnitine replacement and medium chain triglyceride diet has been successful in a number of cases (Class IV evidence).

Defects of beta-oxidation
Defects of fatty acid oxidation may affect muscle alone or in conjunction with other tissue manifestations, i.e. liver and heart (table 37.3). For most of the different enzyme deficiencies, the clinical features are similar. In some patients, this is reflected by exercise-induced muscle pain and rhabdomyolysis. The diagnosis is often suggested by characteristic patterns of organic acids excreted in the urine, which are specific for various enzymatic blocks.

Enzymatic and immunochemical analysis performed in fibroblasts and/or in muscle and liver mitochondria

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Table 37.2 Primary systemic carnitine deficiency.

| Inheritance: autosomal recessive |
| Gene: OCTN2 organic cation transporter |
| Clinical presentation |
| Progressive cardiomyopathy |
| Muscle weakness |
| Fasting hypoglycaemia |
| Urine: normal organic acid pattern |
| Low total carnitine in plasma, urine and muscle |
| Normal ratio carnitine/carnitine-acyl-carnitines |
| Molecular biology: several point mutations reported |

OCTN2, organic cation transporter 2.
Neurological Problems

and their pattern of appearance in plasma and urine is a useful diagnostic test [2]. They are especially important in the diagnosis of beta-oxidation blocks such as VLCAD or MCAD deficiencies.

Other secondary metabolites, produced by enzymatic reactions that free CoA from acyl residues, can be detected in patients’ urine. Glycine derivatives like hexanoyl-glycine or phenylpropionyl-glycine are pathognomonic of MCAD deficiency. The presence of glycine or acylcarnitine derivatives in the urine indicates an increased accumulation of acyl-CoA in the mitochondria. Glutaric aciduria type 2 is pathognomonic of riboflavin-responsive LSM. Fat accumulation in a muscle biopsy depends upon diet and activity level. Analysis of metabolites is a crucial investigation, and can be combined with a study of labelled fatty acid oxidation and appropriate enzyme studies in fibroblasts.

were used to confirm the diagnosis. The use of acylcarnitine and genetics has completely changed the way in which we diagnose the inborn errors of beta-oxidation, which are:

• very long-chain acyl-CoA dehydrogenase (LCHAD or VLCAD) deficiency;
• trifunctional enzyme deficiency;
• medium-chain acyl-CoA dehydrogenase (MCAD) deficiency;
• short-chain acyl-CoA dehydrogenase (SCAD) deficiency;
• riboflavin-responsive disorders of β-oxidation (RR-MADD).

Guidelines for the laboratory diagnosis of fatty acid oxidation defects

Dicarboxylic aciduria is a distinct finding associated with a metabolic block of beta-oxidation. The substrates are converted to dicarboxylic acids by the combined action of omega-oxidation in the endoplasmic reticulum and by peroxisomal beta-oxidation.

The metabolic intermediates accumulating behind the enzymatic block can be detected in urine and blood. Often, they are formed only during a metabolic crisis. The qualitative and quantitative study of the organic acids produced in the patients is indicated by gas chromatography–mass spectrometry (GC–MS) analysis. Acylcarnitines can be revealed in patients with organic aciduria due to the activity of acylcarnitine transferase, and their pattern of appearance in plasma and urine is a useful diagnostic test [2]. They are especially important in the diagnosis of beta-oxidation blocks such as VLCAD or MCAD deficiencies.

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VLCAD deficiency

VLCAD deficiency has mostly been described in children [20]. The patients reported so far can be grouped according to their clinical course: a first group has an onset in the first few months of life and shows a high mortality; a second group is characterized by recurrent episodes of coma after fasting, but presents no cardiomyopathy; a third group presents with late-onset rhabdomyolysis and myalgia after muscle exercise.

Deficient patients cannot oxidize C18 to C16 fatty acids, whereas the oxidation of shorter fatty acids (shorter

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<th>Table 37.3 Clinical features in metabolic defects of fatty acids disorders.</th>
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<td>Cramps</td>
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<td>Systemic carnitine transporter</td>
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<td>Muscle carnitine</td>
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<tr>
<td>CPT II</td>
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<tr>
<td>VLCAD</td>
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<tr>
<td>Trifunctional protein</td>
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<tr>
<td>MCAD</td>
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<tr>
<td>SCAD</td>
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<td>RR-MAD</td>
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CPT II; carnitine palmitoyltransferase deficiency; VLCAD; very long-chain acyl-CoA deficiency; MCAD; medium-chain acyl-CoA deficiency; SCAD; short-chain acyl-CoA deficiency; RR-MAD; riboflavin-responsive multiple acyl-CoA-dehydrogenase.
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sign of cardiomyopathy or myopathy. During the crisis, all patients develop hypoketotic hypoglycaemia, with an increased ratio of free fatty acids to ketone bodies, elevated serum aminotransferases, and mild hyperammonaemia, probably due to increased proteolysis. Plasma and tissue carnitine is low (25% of controls in liver and muscle), with an increased acyl/free carnitine ratio. The secondary carnitine insufficiency observed in MCAD-deficient patients is due not only to an increased excretion of acylcarnitines, with depletion of tissue carnitine, but also to defective reabsorption in the kidney.

**MCAD deficiency**

MCAD deficiency (OMIM number 201450) is the most common error of fatty oxidation found in the USA, UK, and Northern Europe. Patients present with recurrent somnolence, vomiting, coma, hypoglycaemia, fatty infiltration of the liver, and dicarboxylic aciduria. The crises are often precipitated by infections. Patients cannot oxidize the medium-chain fatty acids (C12 to C6). The disorder becomes life-threatening during episodes of stress or fasting (table 37.4), which result in decreased caloric intake or increased catabolism.

MCAD deficiency has been found in cases of Reye-like syndrome, and in some cases of sudden infant death syndrome. The first episodes of the disorder occur in the first 12–18 months of life. Incidence in the two sexes is similar. The mortality rate is 25%, but can reach 60% in cases with a later onset (second year of life). In half the families, there was a high incidence of death in infancy.

Hepatomegaly due to fatty liver has been described in some cases. Seizures have been reported, but patients may have normal development and growth, and no clinical sign of cardiomyopathy or myopathy. During the crisis, all patients develop hypoketotic hypoglycaemia, with an increased ratio of free fatty acids to ketone bodies, elevated serum aminotransferases, and mild hyperammonaemia, probably due to increased proteolysis. Plasma and tissue carnitine is low (25% of controls in liver and muscle), with an increased acyl/free carnitine ratio. The secondary carnitine insufficiency observed in MCAD-deficient patients is due not only to an increased excretion of acylcarnitines, with depletion of tissue carnitine, but also to defective reabsorption in the kidney.

**Molecular biology**

Several laboratories have identified the molecular aetiology of MCAD deficiency as a common point mutation in the locus 1p31 (chromosome 1). The mutation, an A to G transition at nucleotide 985, leads to a substitution of lysine by glutamic acid in the mature protein dehydrogenase. It has been observed that patients with MCAD synthesize a normally sized MCAD precursor, which is usually targetted to the mitochondria. A small group (10%) of mutation carriers is completely asymptomatic.

**Treatment Recommendations**

The treatment is similar in LCHAD and MCAD deficiency: fasting and long intervals between meals should be avoided, a high-carbohydrate, low-fat diet should be administered, and L-carnitine supplementation can be useful in preventing secondary carnitine insufficiency (Class IV evidence).

Prevention is important, considering the high incidence of
Riboflavin deficiency may be due to different mechanisms. Riboflavin enters as a coenzyme not only in acyl-CoA dehydrogenase, but also in complex I and complex II of the respiratory chain. Possible mechanisms of riboflavin deficiency include: (1) decreased cellular riboflavin uptake and decreased flavin adenine dinucleotide (FAD) synthesis; (2) decreased FAD transport into mitochondria; (3) abnormal binding of FAD to apoenzymes; and (4) increased catabolism of FAD for increased FADPase. A biochemical study of mitochondrial and muscle FAD and flavin mononucleotide (FMN) levels reveals different mechanisms in patients with riboflavin deficiency [28]. Most of these patients have shown to have electron-transferring flavoprotein dehydrogenase (ETFDH) deficiency [29, 30].

**SCAD deficiency**

Few patients with SCAD deficiency have been described. In SCAD deficiency, the dicarboxylic aciduria is not striking. Many shorter-chain fatty acid residues are seen, such as ethylmalonic, butyric, and methylsuccinic acids. In these patients, the oxidation of C4 to C6 fatty acids is compromised. As MCAD catalyses 50% of C4 dehydrogenation, the diagnosis may be difficult and may require inhibition of MCAD with specific antisera. SCAD deficiency is associated with different clinical phenotypes: a severe infantile form [25] and a late-onset myopathic picture.

**Riboflavin-responsive multiple acyl-CoA dehydrogenase defects (RR-MADD)**

This is a relatively common LSM presenting in adult life with fluctuating episodes of profound weakness, associated with carnitine insufficiency and glutaric aciduria, and usually underdiagnosed, that responds dramatically to riboflavin [26–28]. Both SCAD and MCAD activity are low in the skeletal muscle and mitochondria of these patients who present with an LSM [26, 27]. Therefore this entity is called riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency (RR-MADD) (table 37.5).

It is difficult to explain the improvement of patients and the enzyme changes observed during riboflavin treatment. Riboflavin deficiency may be due to different mechanisms. Riboflavin enters as a coenzyme not only in acyl-CoA dehydrogenase, but also in complex I and complex II of the respiratory chain. Possible mechanisms of riboflavin deficiency include: (1) decreased cellular riboflavin uptake and decreased flavin adenine dinucleotide (FAD) synthesis; (2) decreased FAD transport into mitochondria; (3) abnormal binding of FAD to apoenzymes; and (4) increased catabolism of FAD for increased FADPase. A biochemical study of mitochondrial and muscle FAD and flavin mononucleotide (FMN) levels reveals different mechanisms in patients with riboflavin deficiency [28]. Most of these patients have shown to have electron-transferring flavoprotein dehydrogenase (ETFDH) deficiency [29, 30].

**Diagnosis**

The presence of the characteristic organic acid pattern in urine and blood from a newborn with non-ketotic hypoglycaemia and metabolic acidosis establishes the diagnosis as glutaric aciduria type II. Urinary organic acid analysis by GC–MS shows an increase in lactic acid, malonic acid, ethylmalonic acid, glutaric acid, adipic acid, 2-hydroxyglutaric acid, suberic acid, sebacic acid, and dodecanedioic acid. The finding of 2-hydroxyglutaric aciduria in such patients is a useful diagnostic point and distinguishes the condition from glutaric aciduria type I (glutaryl-CoA dehydrogenase deficiency), in which 3-hydroxyglutaric is excreted.

Diagnosis in the late-onset cases may be considerably more difficult because metabolic acidosis, the usual indication for examining urine organic acids, may not be

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<th>Table 37.5 Riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency.</th>
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<tr>
<td>Adult onset</td>
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<tr>
<td>Lipid storage myopathy</td>
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<tr>
<td>Low SCAD, MCAD</td>
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<tr>
<td>Low free carnitine, increased acyl-carnitines, glutaric aciduria type 2</td>
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<tr>
<td>Riboflavin responsive</td>
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<tr>
<td>SCAD, short-chain acyl-CoA deficiency, MCAD, medium-chain acyl-CoA deficiency.</td>
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present. Furthermore, the organic aciduria in such patients is considerably less pronounced and is often intermittent, being present only during acute episodes. A wider use of blood acylcarnitine analysis should reduce the number of missed diagnoses. Acylcarnitine analysis can reveal a combined elevation of short-chain (<C6), medium-chain (C6–C14), and long-chain (>C14) acylcarnitines. In RR-MADD, free carnitine in serum is decreased because of the increased acylcarnitine levels.

Other RR-MADD cases can be diagnosed by enzymatic assay and mutation analysis (figure 37.4) of ETFDH, the most frequently involved enzyme [29].

Recommendations

It is important to recognize these patients as they improve after riboflavin treatment (100–200 mg/day). Several cases of LSM-associated beta-oxidation defects have been reported, because of multiple acyl-CoA-dehydrogenase deficiency, that were riboflavin responsive (Class IV evidence). Evidence that a biochemical defect involving the oxidation of short-chain fatty acids causes a deficiency of SCAD, MCAD, and FAD, as well as depletion of FAD co-factors in muscle mitochondria should be sought in most cases, especially in those who are riboflavin responsive [28].

Therapy with riboflavin and a low-fat, low-protein diet is beneficial, although the long-term treatment of patients with late-onset glutaric aciduria type II is still challenging. The emerging consensus is that riboflavin prescription is the first-line treatment for RR-MADD patients. Most reports have advocated combination therapy with riboflavin and carnitine as more effective, although a few reports have noted the ineffectiveness of carnitine. Interestingly, the clinical manifestations of primary carnitine deficiency are sometimes similar to those of RR-MADD, especially during metabolic crisis. Accordingly, supplementation of riboflavin together with carnitine is reasonable for the patients suspected of having RR-MADD, but not yet diagnosed. A more recent study [30] suggested that combination therapy with riboflavin and CoQ10 resulted in some cases in a better long-term outcome compared with riboflavin plus carnitine in patients with the myopathic form of CoQ10 deficiency due to ETFDH mutations. Other drugs, such as glycine, prednisolone, and insulin, have also been studied, but their effectiveness remains uncertain.

Good Practice Points for the treatment of fatty acids disorders

The main caution in defects of mitochondrial beta-oxidation is the avoidance of fasting (Class IV evidence). By not allowing patients with such disorders to become dependent on beta-oxidation, the accumulation of toxic intermediate metabolites is avoided and the development of the most critical symptoms is minimized. Fat consumption should be restricted to 25% of total calories, and the amount of LCFA should be reduced (Class IV evidence). Increased caloric intake from carbohydrates may be necessary during intermittent illness because of increased metabolic demands on the body. A low-fat, high-carbohydrate diet is beneficial in reducing the frequency of rhabdomyolysis in several disorders of fatty
acid metabolism, including CPT II deficiency [31] and trifunctional enzyme deficiency [23]. The current dietary treatment of LCFA defects (high carbohydrates with medium even-chain triglycerides, and reduced long-chain fats) is based on evidence provided by experts’ opinion alone or from descriptive case series without controls. It is difficult to perform double-blind studies to prevent cardiomyopathy, rhabdomyolysis, and muscle weakness.

Conflicts of interest
The authors have no conflict of interest.

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