

参考译文：专家组指南手册：EFNS脂肪酸线粒体功能障碍的诊断和治疗指南

Task force guidelines handbook: EFNS guidelines on diagnosis and management of fatty acid mitochondrial disorders

C. Angelini^a, A. Federico^b, H. Reichmann^c, A. Lombes^d, P. Chinnery^e and D. Turnbull^e

^aDepartment of Neurology, University of Padova, Padova, Italy; ^bDepartment of Neurological and Behavioural Sciences, University of Siena, Siena, Italy; ^cNeurologischen Universitätsklinik Universitätsklinikum Carl Gustav Carus der Technischen Universität Dresden, Dresden, Germany; ^dUnité de Recherche INSERM 153, Hôpital de la Salpêtrière, Paris, France; and ^eDepartment of Neurology, The University of Newcastle upon Tyne, Newcastle upon Tyne, UK

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Guidelines in the diagnosis and current dietary treatment of long-chain fatty acid (LCFA) defects have been collected according to evidence-based medicine. Since the identification of carnitine and carnitine palmitoyltransferase deficiency more than 25 years ago, nearly every enzymatic step required for β -oxidation has been associated with an inherited metabolic disorder. These disorders effectively preclude the use of body fat as an energy source. Clinical consequences can range from no symptoms to severe manifestations including cardiomyopathy, hypoglycaemia, peripheral neuropathy and sudden death. **A diet high in carbohydrates, diet with medium-chain triglycerides and reduced amount of LCFA has a beneficial effect (class IV evidence) and in appropriate deficiency states carnitine and riboflavin are used (good practice points).**

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参考译文：高碳水化合物饮食，饮食含中链甘油三酯并减少长链脂肪酸的摄入能产生有益的临床效果（IV级证据），在适当的缺乏状态下，使用左卡尼汀和核黄素（好的临床实践做法）。

Background

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

according to grades of recommendation for treatment classified in terms of evidence-based medicine. Most guideline recommendations derived in this document are from case reports (class IV evidence), as no large trials have been conducted in fatty acid disorders. These guidelines reflect consensus opinions of experts in the field (good practice points). The consensus was reached analysing series of treated patients and in discussing pre-existing guidelines.

Results

Carnitine palmitoyltransferase II deficiency

In the most typical presentations CPT II deficiency is seen in young adults (Table 1) experiencing episodes of muscle pain and rhabdomyolysis triggered by prolonged exercise or cold. 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 triggered by fasting or cold and consist of pain, stiffness without cramps and highly elevated creatine kinase levels (up to 50 000 U) reflecting muscle necrosis. This may lead to acute renal failure.

Recommendations

Preventing myoglobinuric episodes is important and this can be achieved by avoiding strenuous exercise

Correspondence: Dr Corrado Angelini, Department of Neurology, University of Padova, Padova, Italy (tel.: +39 049 821 3625; fax: +39 049 875 1770; e-mail: corrado.angelini@unipd.it).

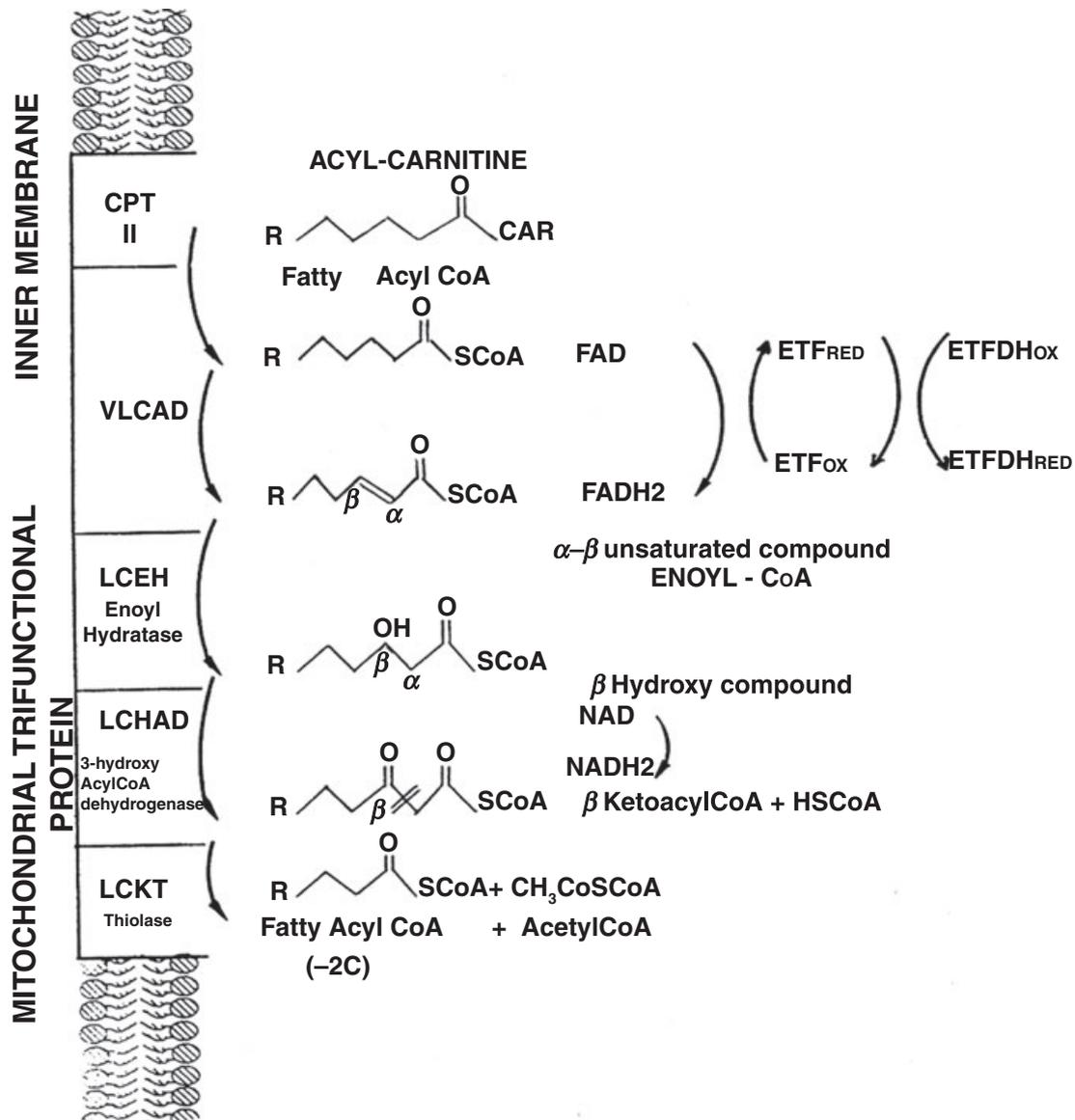


Figure 1 Pathway of long-chain fatty acid oxidation by enzymes in the inner mitochondrial membrane. CPT II, carnitine palmitoyl-transferase II; VLCAD, very-long-chain acyl-CoA dehydrogenase; FAD, flavin adenine dinucleotide; FADH₂, reduced form of FAD; ETF, electron transfer flavoprotein (red = reduced; ox = oxidized); EDFDH, electron transfer flavoprotein dehydrogenase (red = reduce; ox = oxidized); LCEH, long-chain enoyl hydratase; LCHAD, long-chain β -hydroxy acyl-CoA-dehydrogenase; NAD, nicotinamide adenine dinucleotide (NADH₂ = reduced form of NAD); LCKT, long-chain β keto thiolase; CAR, carnitine; CoA, coenzyme A. The other cofactor and enzymes are either in the cytosol or with mitochondrial matrix.

Table 1 Carnitine palmitoyltransferase II (CPT II) deficiency

Young adults
Paroxysmal myoglobinuria
Residual: malonyl-CoA insensitive CPT activity
CPT gene is located in chromosome 1
Serine 113 to leucine is the most common missense mutation
60% cases (429C > T)

during fasting or cold. During an attack 5% of glucose solution is used as an alternative metabolic fuel. According to published guidelines a standard treatment

protocol for myoglobinuria [5] is intravenous infusion of hypotonic sodium chloride and sodium bicarbonate (sodium chloride 110 mmol/l and bicarbonate 40 mmol/l) in 5% of glucose solution to which 10 g of mannitol per litre is added in a 20% of solution. The solution should be infused into a young adult of 75 kg weight at the rate of 12 l/day in order to obtain a diuresis of 8 l/day and keep pH above 6.5. This therapeutic regimen will control both hyperkalemia and acidosis and therefore might prevent acute renal failure.

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 can 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 fatiguability and cardiomyopathy with left axis deviation [6,7]. Primary systemic carnitine deficiency is a well-recognized treatable entity of childhood (Table 2) characterized by progressive cardiomyopathy, LSM and attacks of hypoglycaemia, hepatomegaly with Reye-like syndrome that may lead to permanent brain damage [8].

Diagnosis

In several cases a defect of carnitine 'high-affinity' transport organic cation transporter 2 (OCTN2) gene has been demonstrated in cultured fibroblasts and genomic DNA can be screened for mutations [9,10].

Guidelines for therapy

Carnitine supplementation corrects cardiomyopathy and other clinical signs [6]. In some cases this treatment might avoid cardiac transplant. The L-carnitine dose may vary from 100 to 600 mg/kg/day on the basis of the calculated carnitine depletion from muscle, liver, heart and kidney. Individually adjusted dosing may require plasma level measurement. No side-effects are noted for L-carnitine supplementation except occasional diarrhoea or fishy body odour. In some cases a medium-chain triglyceride (MCT) diet may be added (class IV evidence).

Muscle carnitine deficiency

In primary muscle carnitine deficiency the clinical syndrome is confined to skeletal muscle [11,12]; the clinical features are episodes of fluctuating muscle weakness, affecting mostly limb and neck muscles and severe myalgia.

Table 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/acyl-carnitines
Molecular biology: several point mutations reported

OCTN2, organic cation transporter 2.

Diagnostic guidelines and therapy

The patients show appropriate ketogenesis on fasting and on a high fat 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 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 [12] 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 low muscle content is the result of a genetic defect of the sarcolemmal carnitine transporter. Therefore, muscle carnitine deficiency could be caused by an abnormal low-affinity carrier or

参考译文：

卡尼汀转运缺陷

治疗指南：

补充左卡尼汀能纠正心肌病和其他临床症状[6]。在一些病例中，左卡尼汀治疗能避免心脏移植。补充左卡尼汀的剂量范围为100-600mg/kg/day，应根据卡尼汀从肌肉、肝脏、心脏和肾脏消耗的量来确定。

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 will confirm the diagnosis. Inborn errors of beta-oxidation are:

1. Very long-chain acyl-CoA deficiency (VLCAD)
2. Medium-chain acyl-CoA deficiency (MCAD)
3. Short-chain acyl-CoA deficiency (SCAD)
4. Riboflavin-responsive disorders of beta-oxidation

Guidelines for 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 derived from the enzymatic block can be detected in the urine and blood.

	Cramps	Myoglobinuria	Myalgia	Weakness	Heart	Metabolic crisis
Systemic carnitine transporter	-	-	-	-	+	+
Muscle carnitine	-	-	+	+	-	-
CPT II	±	+	+	-	-	-
VLCAD	-	+	-	-	+	+
Trifunctional protein	-	+	-	-	+	+
MCAD	-	-	-	-	-	+
SCAD	-	-	+	+	-	+
RR-MAD	-	-	-	+	-	+

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.

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. Acyl-carnitines can be revealed in patients with organic aciduria due to the activity of acyl-carnitine-transferase and their pattern of appearance in plasma and urine is a useful diagnostic test [2]. They are especially important in diagnosis of β -oxidation block such as VLCAD or MCAD deficiency. 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 acyl-carnitine 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 the 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.

Very long-chain acyl-CoA-dehydrogenase deficiency

Very long-chain acyl-CoA deficiency has mostly been described in children [13]. The patients reported so far can be grouped according to their clinical course: the first group has onset in the first few months of life and shows a high mortality; the second group is characterized by recurrent episodes of coma after fasting, but presents no cardiomyopathy; the third group presents with late-onset rhabdomyolysis and myalgia after muscle exercise.

Deficient patients cannot oxidize C18 to C16 fatty acids, whereas they can normally utilize shorter fatty acids (shorter than C14). Exercise-induced myoglobinuria is a possible presentation [14,15]. Cardiac involvement is frequent. Other distinctive laboratory

findings include hypoglycaemia, hypoketonuria, high serum ammonia, and slight elevation of serum aminotransferases. Low ketones during severe hypoglycaemia strongly suggest a specific defect of fatty acid oxidation. Liver biopsy, when performed, reveals an increase in both macro- and micro-vesicular fat and mitochondrial abnormalities.

Trifunctional enzyme deficiency

The disease is inherited as an autosomal recessive trait. The common mutation for long-chain β -hydroxy acyl-CoA-dehydrogenase (LCHAD) deficiency is 1538 G > C. Onset of symptoms is in the first year of life, characterized by intermittent hypoglycaemia, lethargy, and coma. The typical presentation is a progressive lethargy, evolving into coma during a fasting or during a febrile episode associated with vomiting and diarrhoea that induces a catabolic state. Hepatomegaly, cardiomyopathy and muscle weakness are usually observed.

Three adult patients from a family with recurrent rhabdomyolysis and peripheral neuropathy were reported [16]. A low-fat/high-carbohydrate diet was beneficial in one patient reducing the frequency of rhabdomyolytic episodes.

Medium-chain acyl-CoA-dehydrogenase deficiency

Medium-chain acyl-CoA deficiency (OMIM number 22274) is the most common error of fatty oxidation found in the US, UK, and Northern Europe. It is manifested by a recurrent syndrome of somnolence, vomiting, coma, hypoglycaemia, fatty infiltration of the liver, and dicarboxylic aciduria. The crises are often precipitated by intercurrent infections. Patients cannot oxidize the medium-chain fatty acids (C12 to C6). The disorder becomes life threatening during episodes of stress or fasting (Table 4), which result in decreased caloric intake or increased catabolism.

Table 3 Clinical features in metabolic defects of fatty acids disorders

Table 4 Medium-chain acyl-CoA-dehydrogenase deficiency

Children
Reye-like syndrome
Fasting hypoglycaemia, non-ketotic
Episodes of coma
Low total plasma carnitine
Decreased tissue carnitine
Decreased octanoic oxidation in fibroblasts
Medium-chain dicarboxylic aciduria
Chromosome 1p31
Common mutation 329 lysine to glutamic acid 90% of cases (986 A > G, K304E)

Medium-chain acyl-CoA 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 both the sexes is similar. The mortality rate is 25% but can reach 60% in cases with later onset (second year of life). In half of the families there was a high incidence of death in infancy.

Hepatomegaly because of 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 increased ratio of free fatty acids (FFA)-to-ketone bodies elevated serum aminotransferases, and mild hyperammonemia, probably because of increased proteolysis. Plasma and tissue carnitine is low (25% of control in liver and muscle), with increased acyl/free carnitine ratio. The secondary carnitine insufficiency observed in MCAD-deficient patients is due to not only increased excretion of acyl-carnitines, with depletion of tissue carnitine, but also 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 with glutamic acid of the mature protein dehydrogenase. It has been observed that patients with MCAD synthesize a normal-size MCAD precursor, which is usually targeted to the mitochondria. A small group (10%) of mutation carriers is completely asymptomatic.

Treatment recommendation

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 (type IV evidence). Prevention is important, considering the high incidence of the disease (1/8930 in a newborn screening programme in Pennsylvania) and the good prognosis in patients under adequate dietary control. The best prevention is the identification of the patients during the asymptomatic period, possibly at birth. Screening of all newborns can be achieved by searching for the typical metabolites in the urine. In Pennsylvania [17], a dry blood spot test on Guthrie cards of newborn babies has been proposed analysing blood acyl-carnitines using GC or MS. On peripheral blood DNA the identification of the A to G mutation, present in 90% of the patients, is obtained by restriction analysis (*NcoI*) of the relevant sequence amplified by the polymerase chain reaction. Data obtained after the initial screening indicate that there is a high prevalence of the mutated allele in babies of German and British heritage, whereas this mutation has been rarely found in newborns of the Mediterranean area. These data suggest that the mutation occurred in a single progenitor of a Germanic tribe. Prenatal diagnosis is possible using the same molecular analysis.

Short-chain acyl-CoA-dehydrogenase deficiency

Few patients with SCAD deficiency have been described. In SCAD deficiency the dicarboxylic aciduria is not striking. Many shorter-chain length 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 [18] and a late-onset myopathic picture.

Riboflavin-Responsive Multiple Acyl-CoA-Dehydrogenase defects

This is a relatively common LSM presenting in adult life with fluctuating episodes of profound weakness, associated with carnitine insufficiency and glutaric

参考译文：

治疗推荐：

中链酯酰辅酶A脱氢酶缺陷 (MCAD) 和长链酯酰辅酶A脱氢酶缺陷 (LCHAD) 的治疗是相似的：应避免禁食和餐间时间间隔太长；接受高碳水化合物，低脂肪饮食；左卡尼汀治疗能有效阻止继发性卡尼汀缺乏症的出现。(IV级证据)

Table 5 Riboflavin-responsive multiple acyl-CoA-dehydrogenase deficiency

Myopathic form
Adult onset
Lipid storage myopathy
Low SCAD, MCAD
Low free carnitine, increased acyl-carnitines, glutaric aciduria type 2
Riboflavin responsive

SCAD, short-chain acyl-CoA deficiency; MCAD, medium-chain acyl-CoA deficiency.

mechanism(s). Riboflavin enters as a coenzyme not only in acyl-CoA-dehydrogenase but also in complex I and complex II of respiratory chain. Possible mechanisms of riboflavin deficiency include (i) decreased cellular riboflavin uptake and decreased flavin adenine dinucleotide (FAD) synthesis; (ii) decreased FAD transport into mitochondria; (iii) abnormal binding of FAD to apoenzymes; (iv) increased catabolism of FAD for increased FADPase. The biochemical study in mitochondria and muscle of FAD and flavin mononucleotide (FMN) levels reveals different mechanism(s) in patients with riboflavin deficiency [21].

Treatment 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 was riboflavin responsive (class IV evidence).

Evidence that a biochemical defect involving the oxidation of short-chain fatty acids causes a deficiency of both SCAD, MCAD and FAD and FMN cofactor depletion in biopsied muscle mitochondria should be sought in most cases, especially in those who are riboflavin responsive [21]

Good practice points for treatment of fatty acid disorders

The main caution in defects of mitochondrial β -oxidation is the avoidance of fasting (class IV evidence). By not allowing patients in such disorders to become dependent for energy needs on β -oxidation, the accumulation of toxic intermediate metabolites is avoided and development of most critical symptoms is minimized. Fat consumption should be restricted to 25% of total calories and have reduced amount of LCFA (class IV evidence). Increased caloric intake from carbohydrates may be necessary during intercurrent illness because of increased metabolic demands on the body. A low-fat/high-carbohydrate diet is beneficial in reducing rhabdomyolytic episodes in several disorders of fatty

acid metabolism including CPT II deficiency [22] and trifunctional enzyme deficiency [16]. The current dietary treatment of LCFAs defects (high carbohydrate with medium-even-chain triglycerid and reduced long-chain fats) is based on evidence provided by expert opinion alone or by descriptive case series without controls. It is difficult to perform double-blind studies to prevent cardiomyopathy, rhabdomyolysis and muscle weakness. A possible alternative diet has been proposed by replacing dietary medium-even-chain fatty acids by medium-odd-chain fatty acids [23], or by precursors of acetyl-CoA such as by the anaplerotic effect of propionyl-CoA* to restore energy production and improve cardiac and skeletal muscle function.

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*The anaplerotic capacity of propionyl-CoA refers to its capacity to provide the formation of methylmalonyl-CoA and energy to the Krebs cycle, because it is a precursor of succinyl-CoA, a citric acid cycle intermediate.

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