14 Disorders of Mitochondrial Fatty Acid Oxidation and Ketone Body Metabolism

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14.1 Introduction

Disorders of mitochondrial fatty acid β-oxidation (FAOD) are a group of inherited metabolic defects that are both clinically and biochemically heterogeneous. Fatty acid oxidation (FAO) is crucial to meet the energy requirement of almost all organs during periods of catabolic stress, and of heart and skeletal muscle at all times. Signs and symptoms in FAOD are mainly due to this inadequacy of energy supply, as well as to potential toxicity of individual metabolites that accumulate secondary to the various enzymatic blocks (for review, Sim et al. 2002).

Therapeutic approaches have two main goals:

- To counteract the accumulation of potentially toxic metabolites such as acyl-CoA esters by preventing lipolysis that occurs during fasting and other catabolic stress, by reducing toxic precursors such as long-chain fatty acids (LC-FA) in long-chain fatty acid oxidation disorders (LC-FAOD), and by promoting detoxification routes such as carnitine esterification
- To circumvent the metabolic block with alternative energetic substrates by providing a high relative amount of carbohydrate, by substituting LC-FA with medium-chain fatty acids in LC-FAOD, by supplying an end-product of β-oxidation such as 3-hydroxybutyrate, or by refilling the Krebs cycle with heptanoate in some disorders, as has recently been described

However, the only two treatment modalities that are undoubtedly beneficial are avoidance of fasting in all FAOD as well as carnitine supplementation for patients affected by carnitine uptake deficiency (OCTN2). The effectiveness of all other therapies has been reported on a case-by-case basis only and provides no firm bases for general recommendations.

14.2 Nomenclature

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
14.1	Carnitine uptake defect	Cardiomyopathy. Reye-like episodes	*OCTN2*	212140
14.2	Carnitine palmitoyl transferase 1	Reye-like episodes/hepatic dysfunction with hypoglycemia. No cardiac, no muscle involvement. Eventually, renal tubular acidosis	*CPT1*	255120
14.3	Carnitine acylcarnitine carrier	Cardiomyopathy, arrhythmia. Liver dysfunction. Unexpected death	*CAC*	212138
14.4	Carnitine palmitoyl transferase 2		*CPT2*	255110
14.4.1	Severe neonatal form	Cardiomyopathy, arrhythmia. Liver dysfunction. Myolysis. Unexpected death. Eventually, renal cysts, multiorgan dysplasias		
14.4.2	Infancy/childhood form	Reye-like episodes. Cardiomyopathy. Myolysis		
14.4.3	Adolescent-adult form	Myopathy, rhabdomyolysis.		
14.5	Very long-chain acyl-CoA dehydrogenase		*VLCAD*	201475
14.5.1	Severe neonatal/early infancy form	Cardiomyopathy, arrhythmia. Liver dysfunction. Myolysis. Unexpected death		
14.5.2	Late infancy/early childhood form	Reye-like episode. Cardiomyopathy. Myolysis. Chronic liver disease		
14.5.3	Adolescent-adult form	Myopathy, rhabdomyolysis		
14.6	Medium-chain acyl-CoA dehydrogenase	Reye-like episodes. Hypoglycemia. A few neonatal/late unexpected deaths	*MCAD*	201450
14.7	Short-chain acyl-CoA dehydrogenase	Poorly defined clinically. Recurrent acute metabolic crises with hypoglycemia, ketoacidosis. Encephalomyopathy, seizures, dysmorphism. Ophtalmoplegia, multicore myopathy (1 case). Ethylmalonate, methylsuccinate (U)	*SCAD*	201470
14.8	Long-chain 3-hydroxyacyl-CoA-dehydrogenase-α		*LCHAD-α*	143450
	Long-chain 3-hydroxyacyl-CoA-dehydrogenase-β		*LCHAD-β*	
14.8.1	Severe neonatal form	Cardiomyopathy, arrhythmia. Liver dysfunction. Myolysis. Unexpected death		
14.8.2	Infancy/early childhood form	Reye-like episodes. Cardiomyopathy. Myolysis. Chronic liver disease (cirrhosis, cholestasis). High incidence of retinopathy, neuropathy. Hypoparathyroidism.		
14.8.3	Adolescent/adult form	Rhabdomyolysis. Neuropathy		
14.9	Medium-/short-chain 3-hydroxyacyl-CoA dehydrogensase	Poorly defined clinically. Fulminant liver disease. Unexpected death (SCHAD in liver). Fasting-induced hypoglycemia (SCHAD in fibroblasts). Hypoglycemia, myopathy, rhabdomyolysis, cardiomyopathy (SCHAD in muscle)	*M/SCHAD*	(600890)

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
14.10	Multiple acyl-CoA dehydrogenation defects		*ETFA* *ETFB* *ETF-DHDH*	231680
14.10.1	Severe neonatal dysmorphic form	Neonatal distress with multiple organ dysplasias (lethal within the 1st week)		
14.10.2	Severe neonatal/early infancy form Milder late infancy/early childhood form	Neonatal distress with hypoglycemia (high mortality rate within weeks) Reye-like episodes. Cardiomyopathy, muscle weakness, myolysis. Progressive leukoencephalopathy		
14.10.3	Late adolescent-adult form	Myopathy, myolysis. Hepatic dysfunction		
14.11	Riboflavin-responsive multiple acyl-CoA dehydrogenation defect	Similar to the milder (14.10.2) or to the late (14.10.3) forms		
14.12	3-Hydroxy-3-methylglutaryl-CoA synthase deficiency	Fasting-induced liver dysfunction with hypoketotic hypoglycemia	*HMGCS2*	246450
14.13	Succinyl-CoA: 3-oxoacid-CoA transferase	Fasting induced ketoacidosis with normal blood glucose levels	*OXCT*	245050
14.14	Long-chain fatty acid transporter protein	Fulminant liver failure (2 cases)	*FATP1*	(600691)
14.15	2,4-Dienoyl-CoA reductase	Myopathy (1 case)	*DECR1*	222745
14.16	Medium-chain 3-ketothiolase	Neonatal distress with hypoglycemia, lactic acidosis, hyperammonemia, myolysis (1 case)	*MKAT*	

14.3 Treatment

■ Management of Life-Threatening Events

No.	Symbol	Therapy	Dosages
14.1	*OCTN2*	L-Carnitine as intravenous infusion	100–400 mg/kg per day
14.2	*CPT1*	Immediate correction of hypoglycemia if present	0.5–1 g/kg per dose
14.3	*CAC*	Constant high-rate glucose infusion (central	
14.4	*CPT2*	intravenous line needed):	
14.5	*VLCAD*	Neonates and infants (<3 years)	10–12 mg/kg per min
14.8	*LCHAD*	Young children (3–10 years)	8–10 mg/kg per min
14.10	*ETF*	Children (> 10 years)	5–8 mg/kg per min
		Insulin infusion (if blood glucose > 6 mmol/l)	0.2–0.3 U/kg per h
		Lipid emulsions are contraindicated	
		L-Carnitine (IV route)	100–200 mg/kg per day
		Once acute problems are resolved, continuous enteral feeding is reintroduced progressively	
14.1	*OCTN2*	For cardiomyopathy and/or cardiac dysrhythmias: conventional cardiac therapy with low NaCl intake, diuretics, cardiotonic and antiarrhythmic drugs	
14.3	*CAC*		
14.4	*CPT2*		
14.5	*VLCAD*		
14.8	*LCHAD*		
14.10	*ETF*		
14.6	*MCAD*	Imediate correction of hypoglycemia if present	0.5–1 g/kg/dose
14.12	*HMGCS2*	Constant high-rate glucose infusion	5–8 mg/kg per min
14.13	*OXCT*	Immediate correction of hypoglycemia if present	0.5–1 g/kg per dose
		Constant high-rate glucose infusion	5–8 mg/kg per min
		Alkalinization if severe acidosis (pH < 7. 20)	Half of daily Na requirement as $NaHCO_3$

During neonatal distress and acute intercurrent decompensations, hypoglycemia, if present, must be corrected immediately by intravenous glucose supply. Subsequently, permanent high-glucose solution is provided in order to maintain blood glucose levels above 5 mmol/l. To meet the recommended glucose infusion rate rapidly, especially in neonates and young children, insertion of a central line catheter should be considered at once. In case of sustained hyperglycemia, insulin infusion is a better choice than decreasing the glucose infusion rate, unless the patient is recovering and continuous enteral feeding can be progressively substituted. In an ETF-DH patient who presented with recurrent life-threatening events with sudden cardiac failure, we have gone further by inserting a permanent central venous line (Port-a-Cath). This measure has allowed immediate high-glucose infusion and rapid recovery in few occasions during the last 3 years.

Lipid emulsions are contraindicated as they contain long-chain fatty acids.

We know now that intravenous carnitine supplementation is well tolerated even by patients with cardiomyopathy or cardiac disrhythmias.

Oral administration of D,L-3-hydroxybutyrate has been successfully used in critically ill ETF patients (disorder 14.10; Van Hove et al. 2003). It could be valuable for all other disorders except OXCT (disorder 14.13).

Cardiomyopathy and dysrhythmias are treated with conventional measures. The potential role of certain antiarrhythmic drugs that inhibit CPT1 activity, such as amiodarone and perhexilline, has been discussed (Bonnet et al. 1999)

It has been proposed to utilize carbamylglutamate (50 mg/kg per day) to treat hyperammonemia that does not regress with high-glucose infusion. However, its usefulness is not proven and one must remember that hyperammonemic states in FAOD are usually not associated with high plasma glutamine levels.

The normalization of glucose, ammonia, plasma free fatty acids, and creatine kinase blood levels is the most valuable indirect marker to indicate that energy metabolism is recovering.

Treatment During Periods of Well-Being

Prevention of Fasting

No.	Symbols	Comments	Therapy
14.2/14.3 14.4.1 14.5.1 14.8.1 14.10.2	CPT1/CAC CPT2 VLCAD LCHAD ETF	In infants <4 months. Severe neonatal/early infancy onset forms	Continuous enteral feeding
(14.2)/14.3 14.4.1/.2 14.5.1/.2 14.8.1/.2 14.10.2	(CPT1)/CAC CPT2 VLCAD LCHAD ETF	Between age 4 months and 24 months; longer in the case of anorexia. Severe early onset forms or milder infant/childhood onset forms	Frequent meals (every 4 h) in daytime + continuous nocturnal enteral feeding
(14.2)/14.3 14.4.1/.2 14.5.1/.2 14.8.1/.2 14.10.2 (14.14.1)	(CPT1)/CAC CPT2 VLCAD LCHAD ETF (FATP1)	Children > 2 years. Severe early onset forms or milder infant/childhood onset forms	Frequent meals in daytime (3 meals and 3 intermeal snacks including a bedtime one) + uncooked cornstarch (1.5–2 g/kg per dose) at midnight
14.2/14.3* 14.4.1/.2* 14.5.1/.2* 14.6/(14.7) 14.8.1/.2* (14.9) 14.10/.2* 14.12 14.13	CPT1/CAC CPT2 VLCAD MCAD/(SCAD) LCHAD (M/SCHAD) ETF HMG-CS2 OXCT	Children older than 4–6 years. Mild childhood-onset forms of FAOD without *signs indicating severe illness such as cardiomyopathy, hepatopathy, or myopathy. Toddlers with ketolysis defects	Normal meal frequency in daytime + a bedtime snack or an uncooked cornstarch dose depending on age (1.5–2 g/kg per dose)
14.2/14.4.3 14.5.3 14.6/14.8.3 14.10.3 14.12 14.13	CPT1/CPT2 VLCAD MCAD/LCHAD ETF HMG-CS2 OXCT	FAOD late adolescent/adult forms. Children with ketolysis defects	Normal meal frequency

Avoidance of fasting is the mainstay of therapy in all FAOD, especially during intercurrent illness. Prescribing increased frequency of meals is a simple preventive measure that allows sufficient glycogen provision that can be used during the first phase of fasting. However, this would not allow infants and young children to cope with night fasting. The maximal time limits for fasting may vary according to age and to the severity of the disorder. Below is some indication of the average tolerance that would be expected in young children,

but the timing should be individualized for each patient, using tolerance tests as described by Morris et al. 1998.

Age	Fasting tolerance (h)
0–4 months	3–4
4–12 months	4–6
1–2 years	6–8
> 2 years	8–12

In young infants with the most severe forms of FAOD, poor appetite, vomiting, and diarrhea may alter the previous scheme. Such cases would benefit from continuous enteral tube feeding for a few months, while others may require nocturnal enteral feeding associated with frequent meals in the daytime. Use of tube feeding in young children has the advantage of allowing prompt nutritional intervention to prevent catastrophic metabolic decompensations during intercurrent illness.

A single dose of uncooked cornstarch given either with a late evening meal or at midnight, depending on individual fasting tolerance, provides a sustained-release source of glucose and may thus delay the fasting period. Usually initiated at 8 months of age, cornstarch is not fully effective before 1 or 2 years. Dosing starts at 1–1.5 g/kg per dose and can be gradually increased to 1.75–2 g/kg per dose by the age of 2 years. It may allow replacement of the nighttime meal or tube feeding in children older than 1–2 years of age (Vockley et al. 2002).

- *Dietary Manipulations*

No.	Disorders (symbols)	Diet (percentage of caloric supply)
14.1, 14.6 14.11 (14.4.3), (14.5.3), 14.7, (14.8.3), (14.10.3) 14.12, 14.13	OCTN2, MCAD ETF-B2+ Mild, late, rhabdomyolytic, asymptomatic forms of (CPT2), (VLCAD), SCAD, (LCHAD), (ETF/ETF-DH) HMGSC2, OXCT	Normal: fat: 30–35%; carbohydrate: 50–55%; proteins: 10–15%
(14.3), (14.4) (14.9) 14.10 (14.14.3)	(CAC), (CPT2) (M/SCHAD) ETF/ETF-DH (MKAT)	High carbohydrate, low fat: fat: 20–25% (including EFA); carbohydrate: 65–75%; proteins: 8–10%
14.2, (14.3), (14.4) 14.5, 14.8, (14.14.1)	CPT1, (CAC), (CPT2) VLCAD, LCHAD, (FATP1)	High carbohydrate, low fat, fat: 20–25%, including: 10% LCT; 10–15% MCT; 1–4% EFA; carbohydrate: 65–75%; proteins: 8–10%

Normal Diet

Many patients do not require a special diet. In a few conditions, namely, OCTN2 (disorder 14.1) and B_2-responsive ETF-DH (disorder 14.11), there are other effective therapies. Patients with MCAD (disorder 14.6), with adult forms of CPT2 (disorder 14.4), with mild-intermittent forms of disorders without chronic expression, with SCAD (disorder 14.7), which clinical expression cannot be clearly linked to the metabolic alteration, and the asymptomatic carriers may tolerate normal diet during periods of well-being. This applies also to ketolysis defect (OXCT, disorder 14.13) and to HMG-CS2 defect (disorder 14.12) that otherwise may require avoidance of protein excesses.

Low-Fat, High-Carbohydrate Diet

A regimen of fat restriction and high carbohydrate (CH) intake, in order to reduce lipolysis, has proven useful for most severe forms of FAOD and is generally recommended. Seventy to seventy-five percent of total energy intakes from carbohydrate are usually recommended.

The ideal proportion of fat intakes has not been studied systematically for each single disease. Many patients are treated with diets providing about 20–25% of total energy intakes as fat (Solis and Singh 2002; Vockley et al. 2002). More severe restriction (<10%) may be applied. It could be an effective means to normalize plasma acylcarnitines profile in deficient LCHAD patients (Gillingham et al. 1999).

Prescription of a fat-restricted diet may put patients at risk of essential fatty acids (EFA) deficiency. Supplementation with EFA can be necessary in order to meet the requirements for age (1–4% of energy intake). Fat-soluble vitamins status has not been studied but may require special attention.

Medium-Chain Triglycerides

Medium-chain triglycerides (MCT) enter mitochondria independently of carnitine. In the LC-FAOD, MCT provision might partially replace the calories that otherwise are provided by LC-FA and thus allow some β -oxidation in the cardiac and skeletal muscles, two tissues that are highly dependent on FAO for their energy requirement. Indeed, a low-fat diet with MCT supplementation, via MCT oil or formulas, is generally used in all LC-FA disorders (Solis and Singh 2002; Vockley et al. 2002). The effectiveness of this approach is controversial and both clinical and biochemical benefits (Parini et al. 1999; Gillingham et al. 1999; Tein 1999) and lack of metabolic alteration have been reported (Lund et al. 2003a).

Some data suggest a role of carnitine acylcarnitine translocase and carnitine palmitoyl transferase 2 in mitochondrial translocation of fatty-acyl esters shorter than C12. Thus, the effectiveness or even the potential harmfulness

roles of MCT-supplementation in CAC (disorder 14.3) and CPT2 (disorder 14.4) patients should be examined carefully (Parini et al. 1999).

Because of the potentially harmful accumulation of toxic metabolites, MCT supplementation is contraindicated in all medium- and short-chain disorders, as well as in ETF/ETF-DH (disorder 14.10), HMG-SC2 (disorder 14.12), and OXCT (disorder 14.13) deficiencies.

There are no universal dosage recommendations for MCT in LC-FA disorders. In LCHAD patients, 10–15% of total energy as MCT (approx. 1.5 g/kg per day), may reduce LC-acylcarnitines accumulation. A higher percentage is not useful, as it would result in medium-chain dicarboxylic aciduria, and MCT in excess would ultimately be stored as LCT in adipocytes (Gillingham et al. 1999).

14.4 Medications

No.	Disorders	Drugs
14.1	OCTN2	100–300 mg carnitine/kg per day
14.2–14.14	All other defects	50–100 mg carnitine/kg per day
14.11	ETF-B2 +	100–300 mg riboflavin (vitamin B_2)/day
14.8	LCHAD α/β	200–400 mg decosahexaenoic acid/kg per day

Carnitine Therapy

In patients affected by OCTN2 (disorder 14.1), L-carnitine therapy is life-saving. It corrects cardiac and skeletal muscle functions within months and allows normal ketogenesis during fasting. With a dosage of 100–300 mg/kg per day divided into three or four doses, plasma carnitine levels can be maintained in the lower normal range (Tein 1999).

In patients with secondary carnitine deficiency, L-carnitine supplementation has long been used. It normalizes plasma carnitine levels and increases urinary excretion of acylcarnitine esters and in this way accelerates the removal of toxic FA intermediates.

In medium- and short-chain FAOD, carnitine levels can be very low as the result of urinary acylcarnitine losses. L-Carnitine supplementation is considered to be beneficial (Wanders et al. 1999; Winter 2003).

In LC-FAOD, L-carnitine supplementation remains controversial because of a theoretical arrhythmogenic risk of LC-acylcarnitine accumulation that has been found in experimental settings. LC-acylcarnitines were also reported to impair the FAO pathway by a substrate/product feedback. In spite of these potential dangers, L-carnitine is commonly prescribed in all FAOD at a median

dose of 75 mg/kg per day, and no deleterious effects have been recognized so far. Direct evidence of a beneficial effect is still lacking, because carnitine is given in combination with other therapeutic measures. However, most patients with LC-FAOD have low plasma free-carnitine levels secondary to increased excretion of LC derivatives, and substitution at pharmacological doses would prevent deficiency and would allow the detoxification process to continue (Gillingham et al. 1999; den Boer et al. 2002; Solis and Singh 2002; Winter 2003).

Riboflavin Supplementation

Because rare patients affected with ETF-DH have been reported with B_2 responsiveness, B_2 supplementation (disorder 14.11), 100–300 mg/day in three divided doses should be systematically tested in these patients.

Docosahexaneoic Supplementation

DHA deficiency has been described with LCHAD defects (disorder 14.8). It has never been described in any other FAOD submitted to low-fat diet. However, conflicting results have been published and not all patients affected with LCHAD (disorder 14.8) are reported to be deficient – even those patients treated with severe restricted-fat diet who have low-to-normal plasma levels of EFA (Gillingham et al. 1999; den Boer et al. 2002). One must, however, remember that EFA should be measured in erythrocytes to conclude on nutritional status (Lund et al. 2003b). Whether putative DHA deficiency could be a contributing factor to the development of neuropathy and retinopathy, exclusively described in LCHAD-deficient patients, is unproven, yet oral supplements are now commonly used.

● *New Therapeutic Approaches*

Triheptanoin

A recent report on this odd-chain triglyceride may open a new pathway to the treatment of LC-FAOD. The rationale for triheptanoin administration relies on the anaplerotic role of the propionyl-CoA obtained during β-oxidation of heptanoate. Propionyl-CoA oxidation forms oxaloacetate and acetyl-CoA that both refill the Krebs cycle, while octanoate and decanoate, as contained in MCT, only give rise to acetyl-CoA. Substitution of triheptanoin for MCT has resulted in dramatic and sustained improvement in three VLCAD patients presenting with severe muscular weakness, rhabdomyolysis and/or cardiomyopathy. It has also allowed the high-carbohydrate diet to be resumed. In theory, a similar improvement might be obtained in other LC-FAOD except for ETF/ETF-DH patients, as in that disorder (disorder 14.10) the generalized dehydrogenation

defect would prevent heptanoate oxidation (Roe et al. 2002). Further studies are underway.

D,L-3-Hydroxybutyrate

The use of 3-hydroxybutyrate is a "product replacement" therapeutic approach in FAOD, during which defective ketogenesis is responsible for energy failure, especially in brain, heart, and muscle.

Beneficial effects have been observed in four patients with the severe infantile form of ETF/ETF-DH (disorder 14.10) who presented with progressive leukodystrophy, or with acute heart failure and myolysis that did not resolve with classic therapy. Oral administration of sodium D,L-3-hydroxybutyrate in increasing doses (100–1000 mg/kg per day) has resulted in sustained clinical and biological improvement (Bonham et al. 1999; Van Hove et al. 2003). This approach might be efficient in all hypoketotic states, especially during acute decompensations. Evidently, it should not be used in patients with ketolysis defect (OXCT/disorder 14.13).

■ Adaptations During Intercurrent Illness

All patients can decompensate rapidly during intercurrent illness and especially during gastroenteritis. To prevent this, a high carbohydrate intake must be maintained during any metabolic stress. Drinks with a 20–25% solution of glucose or cornstarch (patients older than 2 years) should be started at the first sign of illness and then evenly spread over day and night. For those patients usually treated via tube feeding, continuous enteral feeding or repeated bolus of the nutritive solution already used at night can be proposed all through the day. In cases of clinical deterioration with anorexia and gastric intolerance or vomiting, hospital admission is needed for assessment and for intravenous infusion of glucose without delay.

Glucose supply (mg/kg per min)	25% solution	Daily doses
8 (2 years of age)	Maltodextrin	0.8 g/kg/2 h = 12 × 3.2 ml/kg per day
6 (2–6/8 years)	Cornstarch (uncooked)	1.5 g/kg/4 h = 6 × 6 ml/kg per day
5.5 (6/8 years)		2 g/kg/6 h = 4 × 8 ml/kg per day

■ Muscular Forms

Patients who present with late-onset, mild forms with exercise intolerance and vulnerability to rhadomyolysis episodes should, in addition to prevention of fasting, avoid prolonged exercise and cold exposure. A high-carbohydrate diet will replenish muscle glycogen stores and thus help to sustain exercise. Frequent rests and repeated CH loads, via maltodextrin solution or a dose of cornstarch, may be of some benefit (Tein 1999). In practice, it is not easy to plan, and most

patients find their own way to cope with their symptoms. Progressive lethargy with unusual muscular weakness, inability to take oral feedings,and sign of myoglobinuria should prompt rapid hospitalization. Immediate measures to assure energy provision via glucose infusion and/or enteral feeding with a high-carbohydrate, low-fat diet must be taken. Hydration and alkalinization should always be performed to prevent renal failure.

Some beneficial effect of other therapies, such as creatine to prevent recurrent access of myoglobinuria and prednisone in some progressive myopathic forms, has occasionally been reported (Tein et al. 1995; Shortland et al. 2001).

14.5 Follow-up

No.	Disorders	Biological parameter for follow-up
14.1	OCTN2	Free/total carnitine (after an overnight fast)
14.6	MCAD	None available
14.11	ETF-B_2+	None available
14.2 14.3 14.4.1/-2 14.8.1/-2 14.10./-1/-2	CPT1 CAC CPT2 LCHAD α/β ETF*A*/ETFB/ETF-DH	Functional tests to reevaluate fasting tolerance: Blood glucose, lactate, ketones, FA, ammonia, carnitine, acylcarnitines and dicarboxylic acids in urine – Liver function tests, muscle enzymes, EFA/DHA – Cardiac function tests
14.12 14.13	HMGCS2 OXCT	Functional tests to reevaluate fasting tolerance

Clinical assessment will focus on growth, mental development, and cardiac, liver, and muscle function. Regular ophthalmological and neurological evaluations are necessary for LCHAD patients who are susceptible to develop retinopathy and neuropathy. Biological assessment will be regularly planned for those patients affected with severe forms of carnitine shuttle and long-chain mitochondrial spiral defects (Morris et al. 1998; Sim et al. 2002).

14.6 Prognosis

14.1	OCTN2	Good on treatment.
14.6	MCAD	
14.11	ETF-B_2 +	Fasting tolerance would improve with age
14.12	HMG-SC2	
14.13	OXCT	
14.4.3	CPT2 (adult form)	Fairly good, possibly handicapped with myopathy and/or neuropathy
14.5.3	VLCAD (adult form)	
14.8.3	LCHAD α/β(adult form)	
14.10.3	ETF α/β(adult form)	
14.2	CPT1 (infantile/childhood form)	Prognosis uncertain, with high risk of severe sequalae or exitus during intercurrent decompensations
14.3	CAC (infantile/childhood form)	Myopathy, cardiomyopathy
14.4.2	CPT2 (infantile/childhood form)	Myopathy, cardiomyopathy, hepatopathy
14.5.2	VLCAD (infantile/childhood form)	Myopathy, cardiomyopathy, hepatopathy
14.8.2	LCHAD α/β(infantile/childhood form)	Retinopathy, neuropathy, hypoparathyroidism
14.10.2	ETF/ETF-DH (infantile/childhood form)	Myopathy, cardiomyopathy, leukoencephalopathy
14.2	CPT1 (severe neonatal form)	Poor, high risk of sudden death, progressive multi-organ failure, or severe sequelae
14.3	CAC (severe neonatal form)	
14.4.1	CPT2 (severe neonatal form)	
14.5.1	VLCAD (severe neonatal form)	
14.8.1	LCHAD α/β(severe neonatal form)	
14.10.2	ETF/ETF-DH (severe neonatal form)	

As a whole, FAOD are very severe disorders with an unfavorable prognosis. A mortality rate as high as 47% has been reported in a large series of 107 patients. However, in these series and in some LCHAD ones, most of the deaths have occurred at the time of diagnosis and most often before 1 year of age (Gillingham et al. 1999; Saudubray et al. 1999; den Boer et al. 2002). Thanks to better knowledge on clinical presentations, physiopathology, earlier diagnosis and treatment, and novel therapeutic approaches, an increasing number of patients are surviving with a more favorable outcome.

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