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ORIGINAL ARTICLE

Treatment recommendations in long-chain fatty acid oxidation defects: consensus from a workshop

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Summary Published data on treatment of fatty acid oxidation defects are scarce. Treatment recommendations have been developed on the basis of observations in 75 patients with long-chain fatty acid oxidation defects from 18 metabolic centres in Central Europe. Recommendations are based on expert practice and are suggested to be the basis for further multicentre prospective studies and the development of approved treatment guidelines. Considering that disease complications and prognosis differ between different disor-

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ders of long-chain fatty acid oxidation and also depend on the severity of the underlying enzyme deficiency, treatment recommendations have to be disease-specific and depend on individual disease severity. Disorders of the mitochondrial trifunctional protein are associated with the most severe clinical picture and require a strict fat-reduced and fat-modified (medium-chain triglyceride-supplemented) diet. Many patients still suffer acute life-threatening events or long-term neuropathic symptoms despite adequate treatment, and newborn screening has not significantly changed the prognosis for these severe phenotypes. Very long-chain acyl-CoA dehydrogenase deficiency recognized in neonatal screening, in contrast, frequently has a less severe disease course and dietary restrictions in many patients may be loosened. On the basis of the collected data, recommendations are given with regard to the fat and carbohydrate content of the diet, the maximal length of fasting periods and the use of l-carnitine in long-chain fatty acid oxidation defects.

Abbreviations

DHA	docosahexanoic acid
LCHAD(D)	long-chain 3-hydroxy-acyl-CoA dehydrogenase (deficiency)
LCT	long-chain triglycerides (long-chain fat)
MCT	medium-chain triglycerides
MS/MS	tandem mass spectrometry
TFP(D)	mitochondrial trifunctional protein (deficiency)
VLCAD(D)	very long-chain acyl-CoA dehydrogenase (deficiency)

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Introduction

Impairment of energy production from exogenous or endogenous fatty acids is the common feature of all long-chain fatty acid oxidation disorders. Clinical symptoms, therefore, arise or are exacerbated during catabolic situations, e.g. during illness or fasting when lipids are released from endogenous stores. Organs most frequently involved are those using long-chain fatty acids as primary energy source such as the heart and skeletal muscles (Ørngreen et al. 2004). Age at onset, manifestation patterns and clinical severity differ between patients (Andresen et al. 1999; Gregersen et al. 2001; Spiekerkoetter et al. 2004). Long-chain FAO disorders are currently included in newborn screening programmes in many countries and disease prevalence has 'increased' (Wilcken et al. 2003), likely because patients with mild clinical phenotypes are identified in high number, many of whom may only develop clinical symptoms in extreme catabolic situations during severe illnesses. As mass screening by MS/MS identifies many asymptomatic newborns with fatty acid oxidation defects, there is an increasing demand for evidence-based treatment recommendations for these individuals at risk. However, long-term follow-up in screened individuals so far is limited to a maximum of 5–10 years.

During a two-day workshop, metabolic specialists from 18 metabolic centres in Central Europe evaluated outcome and management of 75 patients with long-chain fatty acid oxidation defects as presented in a companion article (Spiekerkoetter et al. 2009). Current treatment strategies for VLCADD and TFP disorders were defined on the basis of expert practice. This is the first report to compare outcome and treatment in patients diagnosed symptomatically and those identified by newborn screening. These data are to be used as a basis for planning future research trials. Also, recommendations on the diagnostic work-up in cases of a positive screening result are given, since the correct classification of the enzyme defect is essential for selection of the appropriate therapy.

General dietary considerations

Fasting guidelines and emergency regimens are the cornerstones of therapy for all FAO disorders. Table 1

Table 1 Suggested maximum fasting periods (during stable metabolic condition)

Neonates	3 hours, also at night
<6 months	4 hours, also at night[a]
>6 months	4 hours at day time, 6 (−8) hours at night[b]
>12 months–3 years	4 hours at day time, 10 (−12) hours at night
4–7 years	4 hours during day, 10 (−12) hours at night

These suggested maximum fasting periods are applicable in healthy infants and children. In situations of illness or metabolic stress, overnight fasting periods should be shorter.
[a] In well-nourished infants overnight fasting can be extended to 6 h from 3 months of age.
[b] In well-nourished infants overnight fasting can be extended to 8 h from 6 months of age.

summarizes the suggested duration of fasting periods according to age. However, these fasting periods apply under healthy, steady-state conditions, when under a normocaloric diet glycogen stores can be built up during the day and used for glucose production during longer fasting intervals at night. In all individuals with long-chain fatty acid oxidation defects, regardless of whether they have ever had any clinical symptoms or not, catabolic states have to be managed by emergency regimens.

For long-chain fatty acid oxidation defects, dietary long-chain fat should be restricted (calculated as a percentage of total energy derived from fat). Long-chain fat intake in healthy infants is 40–45% of total energy, in children of school age 30–35%, according to D-A-CH recommendations (German/Austrian/Swiss Nutrition Societies 2000). With a long-chain fat-restricted diet, additional essential fatty acids have to be supplemented to cover the daily requirements (Table 2). For the optimal ratio of omega 3 to omega 6 fatty acids, walnut oil, soy oil or wheatgerm oil should be preferred.

Routine enrichment of diet with glucose polymers or cornstarch is not recommended, but is part of oral prophylactic and therapeutic emergency treatment. Nasogastric feeding is not generally recommended as part of the long-term treatment, but is recommended during illness with beginning metabolic derangement in attempt to avoid intravenous glucose infusion. However, intravenous emergency therapy should be initiated promptly in more severe illnesses with high fever, recurrent vomiting, or severe gastroenteritis.

Supplementation of vitamins and minerals is generally not necessary. Consumption from food should be calculated and blood concentrations of fat-soluble vitamins and minerals monitored. Supplementation is recommended in cases of low intake or documented deficiency.

Clinical presentation of VLCADD represents the clinically heterogeneous phenotypes of carnitine palmitoyl-CoA transferase II (CPT II) deficiency. Therefore, treatment recommendations for VLCADD could also be very much applicable to CPT II deficiency. Carnitine palmitoyl-CoA transferase I (CPT I) deficiency manifests only with the hepatic phenotype and is phenotypically equivalent to mild VLCADD or even to MCADD.

Dietary recommendations in symptomatic VLCAD deficiency

Symptomatic patients usually receive a long-chain fat (LCT)-restricted and fat-modified diet (modification by MCT supplementation). Long-chain fat content of the diet is suggested to be 25–30% of total energy (Table 3). Since the predominant clinical symptoms in VLCAD-deficient patients during long-term follow-up are episodic muscle pain and rhabdomyolysis suggesting muscular energy deficiency, the diet has to be enriched in MCT to provide 20% of total energy from MCT (Table 3). Patients with exercise-induced muscle pain and weakness benefit from increased MCT (or carbohydrate) supply just prior to more extensive exercise (e.g. in a dose of 0.25–0.5 g MCT/kg).

Table 2 Supplementation of essential fatty acids with a fat-reduced diet (D-A-CH)

Age	Percentage of energy			Walnut / soy / wheatgerm oil (g/day)
	n–6 Linoleic acid	n–3 Linolenic acid	Total	
0 to <4 months	4.0	0.5	4.5	3.5
4 to <12 months	3.5	0.5	4.0	5
1 to <4 years	3.0	0.5	3.5	6
>4 years	2.5	0.5	3.0	10

Table 3 Consensus on dietary regimen in VLCAD deficiency

VLCADD variant	Age	Fat	Carbohydrates	Energy
Asymptomatic (and CK, AST and ALT values within normal limits)	0–4 months	Half breast milk / infant formula, half special low-fat formula • Monogen, SHS Amounts per 100 ml: LCT 0.21 g, MCT 1.89 g or • Basic-f, Milupa + 2.0 g MCT oil per 100 ml Amounts per 100 ml: LCT 0.06 g, MCT 2.00 g	No additional carbohydrates (unless clinically indicated)	No additional energy (according to D-A-CH recommendations)
	After 4 months (introduction of solid food)	Fat reduction to 30–40% of total energy[a] (low values of D-A-CH nutrition recommendations); 10–15% of energy from fat should be from MCT		
Symptomatic	0–4 months	No breast milk or infant formula milk, 100% special low-fat formula • Monogen, SHS Amounts per 100 ml: LCT: 0.21 g, MCT: 1.89 g + essential fatty acids (3.5 g/day) or • Basic-f, Milupa + 2.0 g MCT oil per 100 ml Amounts per 100 ml: LCT 0.06 g, MCT 2.00 g + essential fatty acids (3.5 g/day)	No additional carbohydrates (unless clinically indicated)	No additional energy (according to D-A-CH recommendations)
	After 4 months (introduction of solid food)	Fat reduction to 25–30(−40)% of total energy[a]; 20% of energy from fat should be from MCT[b]; 3–4% of energy from fat should be from essential fatty acids (according to D-A-CH nutrition recommendations)		

MCT, medium-chain triglycerides; LCT, long-chain triglycerides; D-A-CH, German Austrian Swiss dietary recommendations.
[a] Suggested LCT intake in healthy infants is 40–45% of total energy, in children of school age 30–35%, according to D-A-CH recommendations/
[b] In practice, however, LCT intake is higher than suggested because of limited choice of food products; usually only 15% of total energy derives from MCT, another 15% from LCT (including 3–4% essential fatty acids).

Dietary recommendations for individuals with VLCAD deficiency asymptomatic at newborn screening

In asymptomatic VLCAD-deficient patients the necessity of dietary long-chain fat restriction is under debate, because in family screening, after the index case has been detected in newborn screening, asymptomatic 'affected' siblings have been identified, who had never received a fat-reduced diet.

Currently, in asymptomatic VLCAD-deficient infants and children it is recommended to mildly reduce the fat content of the diet to 30–40% of total energy. Individual asymptomatic newborns with VLCADD who completely normalized their acylcarnitine profile after the first week of life have also been treated without a fat-restricted and fat-modified diet in the first months of life and have not developed any VLCAD-associated clinical symptoms so far. Because of molecular heterogeneity in VLCADD, it is very difficult to define clear genotype-phenotype correlation and predict the clinical course of the disease. However, the p.V243A mutation, which has been found on at least one copy in many asymptomatic individuals identified by newborn screening, is typically associated with an attenuated phenotype. Patients with this mutation can develop hypoglycaemia during severe illness or myopathy in connection with stronger exercise, but may also remain asymptomatic. In patients developing only exercise-induced myopathic symptoms later in life, enrichment of the diet with MCT (especially prior to exercise) may be sufficient and LCT restriction may not be necessary.

Dietary recommendations for LCHAD and TFP deficiency

For patients with disorders of the TFP-complex, long-chain fat intake should be as low as possible in both asymptomatic and symptomatic patients for the prevention of long-term neuropathic symptoms. Therefore, in newborns a special infant formula low in LCT and high in MCT (MCT-containing formula) seems mandatory (Table 4). MCT-containing special formula (e.g. Monogen, SHS; or Basic-f, Milupa, + MCT oil) covers all dietary requirements. However, additional supplementation of essential long-chain fatty acids is necessary with these preparations.

In view of the high mortality rate in disorders of the TFP-complex in the first days and weeks of life, dietary treatment in patients detected by newborn screening should generally be initiated immediately after the screening results become available, and even

Table 4 Consensus on dietary regimen in disorders of the TFP-complex

Disorder of TFP-complex	Age	Fat	Carbohydrates	Energy
Asymptomatic **or** symptomatic	0–4 months	No breast milk or infant formula milk, 100% special low-fat formula • Monogen, SHS Amounts per 100 ml: LCT 0.21 g, MCT 1.89 g + essential fatty acids (3.5 g/day) **or** • Basic-f, Milupa + 2.0 g MCT oil per 100 ml Amounts per 100 ml: LCT 0.06 g, MCT 2.00 g + essential fatty acids (3.5 g/day)	No additional carbohydrates (unless clinically indicated)	No additional calories (according to D-A-CH recommendations)
	After 4 months (introduction of solid food)	Fat reduction to 25–30% of total energy[a]; 20–25% of energy from fat should be from MCT[b]; 3–4% of energy from fat should be from essential fatty acids (according to D-A-CH recommendations). Keep LCT intake (other than essential fatty acids) as low as possible!		

[a] Suggested LCT intake in healthy infants is 40–45% of total energy, in children of school age 30–35%, according to D-A-CH recommendations/
[b] In practice, however, LCT intake is higher than suggested because of limited choice of food products; usually only 15% of total energy derives from MCT, another 15% from LCT (including 3–4% essential fatty acids).

before confirmation of diagnosis is achieved by enzyme or molecular analyses.

With start of solid food in patients with disorders of the TFP-complex, long-chain fat content of the diet is suggested to be 25–30% of total energy, with 20–25% as MCT and 5–10% as LCT.

L-Carnitine supplementation

Supplementation of l-carnitine is controversial. There is no published evidence that carnitine is beneficial in long-term treatment of long-chain fatty acid oxidation defects. In view of potential adverse effects, supplementation at time of severe metabolic derangement should be avoided.

Docosahexanoic acid supplementation

In disorders of the TFP-complex including LCHADD, supplementation of docosahexanoic acid (DHA) is recommended at a dose of 60 mg/day in children weighing <20 kg and a dose of 120 mg per day in children >20 kg body weight.

Monitoring of treatment

In all patients with long-chain fatty acid oxidation defects, careful follow-up investigations in metabolic centres have to be performed, irrespective of the severity of the defect and the choice of treatment.

Effectiveness of treatment is indicated by reversal of clinical symptoms and normalization of creatine kinase and transaminases, as well as reduced production of disease-specific long-chain acylcarnitines. Creatine kinase and transaminases are, therefore, ideal markers that can be used for monitoring of treatment. Free carnitine in blood can also serve as a parameter for monitoring in unsupplemented patients, indicating the amount of acylcarnitines formed for excretion in bile and urine and the concurrent loss of free carnitine. In fact, free carnitine concentrations in blood fluctuate between reduced and normal in patients not supplemented with l-carnitine. Monitoring of patients with long-chain fatty acid oxidation defects should also include echocardiography and documentation of liver size and structure once a year. In disorders of the TFP-complex, yearly ophthalmological investigations (electroretinography) are necessary to assess signs of retinopathy. Yearly assessment of nerve conduction velocity is also suggested in disorders of the TFP-complex.

Diagnostic work-up after a positive screening result

Confirmation of diagnosis should be done primarily by enzyme analysis in lymphocytes. For most of the long-chain fatty acid oxidation defects, enzyme analysis is feasible in lymphocytes, but, owing to molecular heterogeneity, mutation analysis in most disorders is laborious and expensive. For disorders with a prevalent mutation, such as isolated LCHADD with the homozygous c.1528G>C mutation, diagnosis can be confirmed by molecular analysis.

Discussion and conclusions

Evidence-based treatment recommendations for disorders of long-chain fatty acid oxidation are not available (Solis and Singh 2002). Based on expert opinion, this is the first approach defining disease-specific dietary recommendations for patients with VLCADD and TFP disorders, distinguishing between symptomatic and asymptomatic patients. Heterogeneity of clinical phenotypes has long been reported (Gregersen et al. 2004) and since newborn screening it also comprises asymptomatic presentations (Spiekerkoetter et al. 2003). Aside from this, molecular heterogeneity does not allow prediction of disease severity or outcome at time of newborn screening.

According to the treatment protocol suggested here, feeding with breast milk or infant formula should be continued in asymptomatic individuals with VLCADD if routine laboratory results such as creatine kinase, liver function test and glucose are within normal limits. Whether a long-chain fat-restricted diet is required at all in these mild phenotypes or whether regular feeding and MCT supplementation, especially in situations of increased energy demand, is sufficient has to be evaluated by longer follow-up investigations (Spiekerkoetter 2007). Episodic muscular symptoms such as rhabdomyolysis are pathogenetically attributed to energy deficiency, and symptoms are reversed by sufficient energy supply in the form of carbohydrates or MCT (Gillingham et al. 2006). It has been reported that exercise-induced rhabdomyolysis in particular can be prevented by sufficient MCT-intake just prior to exercise (Gillingham et al. 2006; Spiekerkoetter 2007). Gillingham and colleagues also reported positive effects of higher dietary protein intake on energy balance and metabolic control in children with LCHADD or TFPD (Gillingham et al. 2007).

Peripheral neuropathy and retinopathy attributed to neuropathic optic changes in disorders of the TFP-complex are most likely due to toxic effects of accumu-

lating long-chain 3-hydroxyacylcarnitine or acyl-CoA compounds. Based on this, long-chain fat intake has to be as restrictive as possible in these patients, also in asymptomatic individuals at time of diagnosis. In previous studies it was hypothesized that retinopathy is caused by deficiency of essential fatty acids, especially deficiency of DHA. According to a recent survey from Gillingham and colleagues (Gillingham et al. 2005) optimal dietary therapy as indicated by low plasma 3-hydroxyacylcarnitine and high plasma DHA concentrations was associated with retention of retinal function and visual acuity in children with LCHAD or TFP deficiency.

In the past, supplementation with l-carnitine was proposed in fatty acid oxidation defects for detoxification of accumulating long-chain acyl-CoA esters. Nowadays, l-carnitine supplementation is more controversial. Recent data on carnitine homeostasis in the mouse model of VLCADD demonstrated that l-carnitine supplementation significantly induces production of long-chain acylcarnitines without replenishing low-free carnitine concentrations in tissues (Liebig et al. 2006; Primassin et al. 2008). In disorders of the TFP-complex, supplementation of l-carnitine may therefore induce further production of 3-hydroxyacylcarnitines that are potentially responsible for the irreversible neuropathic symptoms. Studies in the VLCAD-deficient mouse model further demonstrated that endogenous carnitine biosynthesis is induced with increased carnitine demand (Primassin et al. 2008), but is suppressed by exogenous l-carnitine supplementation. In the mouse, intermittent low free carnitine concentrations in tissues and blood can be well replenished by endogenous carnitine production (Primassin et al. 2008). In many patients with long-chain fatty acid oxidation defects off l-carnitine supplementation, free carnitine concentrations in plasma also fluctuate between low and normal, demonstrating endogenous carnitine biosynthesis in humans as well. In summary, l-carnitine supplementation has to be considered with care, especially in patients with disorders of the trifunctional protein. There is consensus, however, to abandon in particular intravenous l-carnitine application during acute metabolic derangements because of significant production of potentially toxic acylcarnitines in these situations that have resulted in sudden death.

In conclusion, treatment recommendations for long-chain fatty acid oxidation defects have to be disease-specific. The degree of dietary long-chain fat restriction has to be well adapted to the severity of the underlying enzyme defect. Whether new treatment strategies such as bezafibrates (peroxisome proliferator activated receptor alpha (PPARα) agonists) (Gobin-Limballe et al. 2007) have an additional role in the therapeutic regimen will be subject of further studies.

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