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Recognition and management of fatty acid oxidation defects: A series of 107 patients

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Summary: In a personal series of 107 patients, we describe clinical presentations, methods of recognition and therapeutic management of inherited fatty acid oxidation (FAO) defects. As a whole, FAO disorders appear very severe: among the 107 patients, only 57 are still living. Including 47 siblings who died early in infancy, in total 97 patients died, of whom 30% died within the first week of life and 69% before 1 year. Twenty-eight patients presented in the neonatal period with sudden death, heart beat disorders, or neurological distress with various metabolic disturbances. Hepatic presentations were observed in 73% of patients (steatosis, hypoketotic hypoglycaemia, hepatomegaly, Reye syndrome). True hepatic failure was rare (10%); cholestasis was observed in one patient with LCHAD deficiency. Cardiac presentations were observed in 51% of patients: 67% patients presented with cardiomyopathy, mostly hypertrophic, and 47% of patients had heart beat disorders with various conduction abnormalities and arrhythmias responsible for collapse, near-miss and sudden unexpected death. All enzymatic blocks affecting FAO except CPT I and MCAD were found associated with cardiac signs. Muscular signs were observed in 51% of patients (of whom 64% had myalgias or paroxysmal myoglobinuria, and 29% had progressive proximal myopathy). Chronic neurologic presentation was rare, except in LCHAD deficiency (retinitis pigmentosa and peripheral neuropathy). Renal presentation (tubulopathy) and transient renal failure were observed in 27% of patients. The diagnosis of FAO disorders is generally based on the plasma acylcarnitine profile determined by FAB-MS/MS from simple blood spots collected on a Guthrie card. Urinary organic acid profile and total and free plasma carnitine can also be very helpful, mostly in acute attacks. If there is no significant disturbance between attacks, the diagnosis is based upon a long-chain fatty acid loading test, fasting test, and *in vitro* studies of fatty acid oxidation on fresh lymphocytes or cultured fibroblasts. Treatment includes

avoiding fasting or catabolism, suppressing lipolysis, and carnitine supplementation. The long-term dietary therapy aims to prevent periods of fasting and restrict long-chain fatty acid intake with supplementation of medium-chain triglycerides. Despite these therapeutic measures, the long-term prognosis remains uncertain.

Since the description of carnitine and muscle carnitine palmitoyltransferase deficiency 25 years ago (Di Mauro and Di Mauro 1973; Engel and Angelini 1973), defects of fatty acid oxidation (FAO) have become one of the most important group of inherited disorders, with a broad clinical spectrum varying from severe malformations or sudden infant death to almost asymptomatic adults. Despite the relative abundance of new case reports, there is evidence that many of these disorders remain misdiagnosed owing to the diversity of presenting signs and the need to collect blood and urine specimens for metabolic investigation at an appropriate time in relation to the illness. As the mitochondrial oxidation of fatty acids is critical in supplying energy during periods of fasting and catabolism, most of the disorders affecting the mitochondrial FAO pathway can produce very severe life-threatening events such as cardiac arrest, collapse and sudden infant death. Some intermittent abnormalities that occur rapidly and are reversible do not allow any collection of blood and urine samples at the time of acute attacks.

We describe here the clinical presentations of inherited mitochondrial FAO disorders mostly based upon our personal experience of 107 patients, most of whom were observed within the last 25 years in our institution, Hôpital Necker Enfants-Malades, Paris. These patients were affected with the following defects: 10 carnitine transporter (CT); 9 carnitine palmitoyltransferase I (CPT I); 15 carnitine palmitoyltransferase II (CPT II); 10 translocase (TL); 12 very long-chain acyl-CoA dehydrogenase (VLCAD); 5 trifunctional (TF); 10 3-hydroxy long-chain acyl-CoA dehydrogenase (LCHAD); 9 medium-chain acyl-CoA dehydrogenase (MCAD); 15 multiple acyl-CoA dehydrogenase deficiency (MAD) due to electron-transfer flavoprotein (ETF) and electron-transfer flavoprotein dehydrogenase (ETFDH); and 12 unclassified defects. For all patients the diagnosis of FAO disorder was verified by following the oxidation of 1-^{14}C fatty acids to $^{14}CO_2$ and the dehydrogenation of 9,10-^{3}H fatty acids by lymphocytes and/or fibroblasts (Brivet et al 1995; Saudubray et al 1982). In most of the cases, the diagnosis was confirmed by a specific enzyme assay.

CLINICAL FEATURES

Characteristic and revealing symptoms (Table 1)

As a whole, FAO disorders appear very severe, since in 43% of families there was at least one death in the sibship. Among the 107 patients, only 57 are still living. In total, 97 died (50 propositus and 47 siblings), of whom 30% were within the first

Table 1 Characteristic and revealing symptoms (89 families, 107 patients)

Sex ratio: male/female	56/51	
Consanguinity	30/107 (28%)	
Sibling's death	47/107 (43%)	
Sibling's age at death		
<8 days	11/47 (23%)	
8 days–1 year	18/47 (38%)	
>1 year	11/47 (23%)	
Unknown	7/47 (16%)	
Patients still living	57/107 (53%)	
	At onset	*At death*
Age:	(n = 107)	(n = 50)
<1 month (most before 8 days)	34 (30%)	18 (36%)
1 month–1 year	34 (31%)	20 (40%)
1–2 years	14 (13%)	4 (8%)
>2 years	17 (16%)	6 (12%)
Unknown	8 (10%)	2
Revealing symptoms		
Neonatal neurological distress	25 (23%)	
Hypoketotic hypoglycaemia	49 (31)[a] (46%)	
Coma (after 1 month)	32 (30%)	
Reye syndrome	18 (17%)	
Heart beat disorders	15 (10)[b] (14%)	
Cardiomyopathy	13 (12%)	
Sudden death	7[c] (7%)	
Near-miss (collapse, respiratory arrest)	7 (7%)	
Myolysis, myoglobinuria	6 (6%)	
Muscle weakness	2 (2%)	
Isolated hepatomegaly	2 (2%)	
Cholestasis	1	

[a] Onset after 1 month
[b] Without associated cardiomyopathy, all in neonatal period
[c] All in neonatal period

week of life and 69% before 1 year. A large majority of patients presented in early infancy (84% before 2 years of age, of whom approximately one-third were in the neonatal period before 3 days of life). In infancy and childhood, the most frequent late-onset revealing symptoms are hypoketotic hypoglycaemia (46%), coma triggered by fasting or catabolism (30%), Reye syndrome-like episodes (17%), cardiomyopathy (12%) (most due to carnitine uptake deficiency), and acute attacks of myolysis and myoglobinuria (6%) (all with CPT II deficiency). Only two patients were primarily referred for muscle weakness. Two patients presented with isolated hepatomegaly and one (affected with LCHAD) was referred to our unit at 6 months of age for a severe cholestasis (see below, hepatic signs).

Neonatal symptoms (Table 2)

Four main neonatal presentations were observed — malformations and facial dysmorphia, sudden death, heart beat disorders, and neurological distress — which were diversely combined.

Facial dysmorphia (Zellweger-like face, low-set ears, high forehead, wide-spaced eyes), renal dysplasia and renal cysts, and brain malformations and dysplasia are observed in MAD (Bohm et al 1982; Colevas et al 1988; Wilson et al 1989) and in CPT II deficiencies (Witt et al 1991; Hug et al 1991). These findings emphasize the role of prenatal energy deprivation as a mechanism of malformations (Freinkel et al 1984).

Sudden death was observed in 7 patients in the sibships, in which there were 22 siblings who died in the neonatal period with unexpected or sudden death. This emphasizes the importance of searching systematically for FAO disorders in such circumstances. The most frequent disorders involved are CPT II, translocase, trifunctional, VLCAD, MAD and MCAD defects (Boles et al 1998; Harpey et al 1987).

Heart beat disorders (arrhythmia and conduction defects) have been observed as common symptoms in the neonatal period in 10 patients affected with CPT II, translocase, trifunctional, VLCAD, or MAD deficiencies. In most cases, heart beat disorders were associated with neurological distress.

Neurological distress was observed as a preponderant sign in 28 patients (26% of our series). The most important clinical signs were lethargy, coma and hypotonia, associated with liver and/or cardiac symptoms such as heart beat disorders and cardiomyopathy. According to our classification of inborn errors of metabolism in the neonatal period (Saudubray and Charpentier 1995; Saudubray et al 1989), patients can be classified as type II (neurological distress with predominant hypoketotic hypoglycaemia and metabolic acidosis: 7 patients); type III (neurological distress with predominant lactic acidosis: 7 patients affected with trifunctional or MAD deficiencies); type IVA (neurological distress with predominant or isolated hyperammonemia: 6 patients affected with CPT II, translocase or trifunctional deficiencies; in two of these the first diagnosis considered was a urea cycle defect); and type IVB (neurological distress without any metabolic disturbance: 8 patients affected with trifunctional, translocase, VLCAD or MCAD deficiencies).

Hepatic symptoms

Hepatic symptoms were found in 73% of our patients. Hypoketotic hypoglycaemia was found in 80% of the patients with hepatic signs. In most cases, the inappropriately low levels of plasma ketones were suggested by negative acetest in urine at the time of acute attack and then further demonstrated by a carefully supervised fasting test (Bonnefont et al 1990; Bougnères et al 1981). Although in neonates hypoglycaemia never raised a real diagnostic problem, in infancy, by contrast, diagnosis of hyperinsulinism, hypopituitarism and fructose bisphosphatase deficiency were considered and ruled out, before reaching the correct diagnosis of FAO disorder. In 37% of patients with hepatic signs, Reye syndrome was the first manifestation of the

Table 2 Fatty acid oxidation disorders: clinical features in 107 patients

Malformations, dysmorphology	5 (4.6%)	CPT II, MAD
Facial dysmorphia (Zellweger-like face, low-set ears, high forehead, wide spaced eyes)	5	
Renal dysplasia	3	
Brain malformation, dysplasia	0	
Acute neonatal presentations		
Sudden death	7 (7%)	CPT II, TL, TF, VLCAD, MAD
Heart beat disorders	10 (11%)	CPT II, TL, TF, VLCAD, MAD
Neurological distress: lethargy, coma, hypotonia, with liver and/or cardiac signs (heart beat disorders, cardiomyopathy)	28 (26%)	
Type IIb (with predominant hypoketotic hypoglycaemia and metabolic acidosis)	7 (6%)	CPT 1, CPT II, TL, MAD, VLCAD
Type III (with predominant lactic acidosis)	7 (6%)	TF, MAD
Type IVa (with predominant hyperammonaemia)	6 (5%)	CPT II, TL, TF
Type IVb (without any metabolic disturbance)	8 (8%)	TL, TF, VLCAD, MCAD
Hepatic presentations	78 (73%)	All disorders
Steatosis	36/38 (95%)	All disorders
Hypoketotic hypoglycaemia	63/78 (80%)	All disorders
Hepatomegaly	39/78 (50%)	All disorders
Reye syndrome	29/78 (37%)	All disorders
Hepatic failure (PT < 35%)	9/78 (11%)	MAD, TL
Cholestasis	1/78 (1%)	LCHAD
Cardiac presentations	55 (51%)	All but CPT I and MCAD
Cardiomyopathy	37/55 (67%)	All but CPT I and MCAD
Hypertrophic	22/37 (60%)	All but CTD
Dilated	10/37 (27%)	CTD, TF
Unknown	5/37 (13%)	
Heart beat disorders	26/55 (47%)	All but CPT I, CTD, MCAD
Without cardiomyopathy	14/26 (54%)	
Conduction abnormalities (LBBB, AVB, sinus node dysfunction)	10/26 (40%)	
Arrhythmias (VT, VF, SVT)	21/26 (80%)	
Collapse	17/55 (31%)	All but CPT I, MCAD, CTD
With near-miss (respiratory arrest)	7/17 (40%)	

Muscular signs	44 (41%)	All but CPT I and MCAD
Myalgia, myolysis, paroxystic myoglobinuria, elevated CK	28/44 (64%)	CPT II, TL, TF, VLCAD, LCHAD, MAD, SCHAD
Severe muscular hypotonia with respiratory distress (neonatal)	5/44 (11%)	TF
Progressive proximal myopathy	13/44 (29%)	CTD, TF, LCHAD, VLCAD
Chronic neurological presentation	14/107 (13%)	Mostly LCHAD
Retinitis pigmentosa	4	LCHAD (4/10)
Peripheral neuropathy	2	LCHAD (2/10)
Mental retardation, neurological sequelae (mostly after Reye)	8	CPT I, CPT II, LCHAD, MAD, VLCAD
Renal presentation	22/107 (20%)	All but CTD, MCAD
Tubulopathy	6/22 (27%)	CPT I, CPT II, LCHAD, MAD
Acute and transient renal failure	13/22 (59%)	All but CTD, MCAD
Renal cysts	3/22 (13%)	CPT II, MAD
Enlarged kidneys	6/22 (27%)	CPT II, MAD, CPT I
Miscellaneous		
Anaemia	3/107	CTD (3/10)
Salt-losing syndrome (neonatal and transient)	1/107	CPT II
Hypoparathyoidism (not observed in our series)		LCHAD, TF
Stridor (not observed in our series)		MAD riboflavin-responsive
Acute fatty liver and HELLP syndrome in pregnancy (not observed in our series)		LCHAD, CPT I
EPEMA syndrome (encephalopathy, petechiae, acrocyanosis, recurrent attacks, ethylmalonic aciduria) (not observed in our series)		
Asymptomatic (very frequent in MCAD even with the common homozygote mutation at the codon 985)		MCAD, others ?

Disorders: carnitine transporter defect (CTD); carnitine palmitoyltransferase I (CPT I); carnitine palmitoyltransferase II (CPT II); translocase (TL); very long-chain acyl-CoA dehydrogenase (VLCAD); trifunctional protein (TF); 3-hydroxy long-chain acyl-CoA dehydrogenase (LCHAD); medium-chain acyl-CoA dehydrogenase (MCAD); multiple acyl-CoA dehydrogenase deficiency (MAD)

disease. A moderate hepatomegaly was very frequent during an acute attack (3–6 cm below the costal margin), associated with fasting hypoglycaemia, negative inappropriately low urine test for ketones, mild acidosis (serum bicarbonates < 15 mmol/L), mild hyperlactacidaemia (2–6 mmol/L), mild hyperammonaemia (80–200 μmol/L), slightly prolonged prothrombin time (around 50%) and moderately increased serum transaminases (100–800 U/ml). In all cases, bilirubin was normal. In our series, there were no clinical, biological, or histological criteria which allowed us to separate *a priori* FAO disorders from idiopathic Reye syndrome. All kinds of FAO disorders can present with Reye syndrome, hepatomegaly, steatosis and hypoketotic hypoglycaemia.

By contrast, true hepatic failure (prothrombin time < 35%) was a rather rare finding in our series (11%) and was only observed in MAD and translocase deficiencies. One unique patient was referred at 6 months of age with an acute liver dysfunction characterized by jaundice, pale stools, firm hepatomegaly, cholestasis (high bilirubin and γ-GT, slight elevation of transaminases, normal platelet function), and axial hypotonia with intermittent loss of consciousness secondary to hypoglycaemia. Liver biopsy showed some degree of portal fibrosis and large vacuoles of steatosis. This patient was affected with LCHAD deficiency. All symptoms improved dramatically within 1 month after institution of a low long-chain fat diet with supplementation of medium-chain triglycerides. This presentation has already been described in LCHAD (Hale and Bennett 1992; Hale et al 1990a; Riudor et al 1986; Rocchiccioli et al 1990).

Cardiac presentations

Cardiac signs were observed in 55 patients (51%) affected with all varieties of FAO disorders, except CPT I and MCAD. Progressive cardiomyopathy, mostly hypokinetic hypertrophic, was found in 37 patients (67% of all cardiac presentations). It was a revealing sign in 10 patients with carnitine transporter defects. In 2 patients the diagnosis was so late that they presented to the emergency department almost at an end stage of cardiac failure with dilated hypokinetic cardiomyopathy. They were referred to the cardiology unit for consideration of cardiac transplantation. With the exception of these two patients, cardiomyopathy in all other patients was most evident on echocardiography, which showed poor activity and thickened ventricular walls. In all patients with carnitine transporter defect, cardiomyopathy improved dramatically on carnitine therapy with a complete recovery of ventricular functions within 6–12 months.

Interestingly, heart beat disorders were observed in 26 patients (47% of all cardiac presentations). All kinds of conduction abnormalities (bundle branch block, auriculo-ventricular block, sinus node dysfunction) and arrhythmias (ventricular tachycardia, supraventricular tachycardia, ventricular fibrillation) were observed. Of these patients, 54% had no clinical or echocardiographic signs of cardiomyopathy, so that heart beat disorders were the only cardiac expression in these patients. As already mentioned, heart beat disorders were the only revealing signs in several patients in the neonatal period. These heart beat disorders were never observed in

carnitine transporter defects or in CPT I or MCAD patients. Conversely, they were very frequent in severe forms of CPT II, translocase, VLCAD, LCHAD and trifunctional enzyme deficiencies, conditions in which there is an obvious accumulation of long-chain acyl-CoA and acylcarnitine (Corr et al 1989). These heart beat disorders can be responsible for collapse with near-miss and respiratory arrest or sudden infant death, mostly in the neonatal period and in infancy. They can easily be misdiagnosed as toxic shock or malignant hyperthermia.

Muscular symptoms

Thirty-four (41%) of our patients affected with all kinds of FAO disorders, except CPT I and MCAD, presented with significant muscular signs. Progressive muscular weakness, mostly proximal, with lipid deposits was a predominant symptom in 13 patients, among whom 4 were severely amyotrophic (all four were affected with carnitine transporter defect). Episodic muscle pain, rhabdomyolysis, elevated creatine kinase (permanent or intermittent) and myoglobinuria triggered by catabolic stresses such as prolonged exercise, fasting, cold exposure, or intercurrent infections, were observed in 28 patients, mostly CPT II, translocase, LCHAD, VLCAD and MAD patients. We did not observe any patient with SCHAD deficiency (Tein et al 1991). Permanent muscle pain and weakness, even at rest, were observed in 3 adolescent CPT II patients. In 2, pain started shortly after a light exercise in the group of working muscles and thereafter diffused rapidly to all other muscles not involved in the effort, including those of the spine and of the neck, suggesting a process secondary to a diffusible factor. A very severe generalized neonatal hypotonia was the presenting symptom in 5 patients with trifunctional enzyme deficiency that clinically mimicked congenital myopathy.

It must be stressed that no muscle symptom was observed in CPT I and MCAD patients. In CPT I, this is related to a muscular-specific isoform of CPT I that is not deficient in hepatic CPT I deficiency (Tein et al 1989).

Neurological symptoms

Only a few chronic neurological signs were observed in our series (14 patients). Severe retinitis pigmentosa was found in 4 of the 10 LCHAD-deficient patients, and progressive peripheral neuropathy in 2 of these. This very unusual presentation seems to be very frequent, if not constant, in this disorder, and is also highly specific to this disorder because it has never been observed in other mitochondrial fatty acid oxidation disorders (Dionisi-Vici et al 1991; Hale et al 1990b; Poll-The et al 1988). Pathophysiology of this retinal dysfunction is not well understood but could be related to docosahexanoic acid (DHA) deficiency. A preliminary therapeutic attempt to treat LCHAD patients with oral DHA supplementation suggests partial efficacy assessed by standard acuity testing, visual evoked potentials and electroretinography (Harding et al 1998).

Mental retardation and neurological sequelae were observed mostly in patients with Reye syndrome-like encephalopathy (mostly CPT I, CPT II, LCHAD, MAD

and VLCAD). Acute encephalopathy (in the neonatal period or as recurrent late-onset attacks) was observed in several patients independently of Reye syndrome or hypoglycaemia. The occurrence and pathophysiology of this neurological symptom are unclear.

Renal presentation

Transient tubulopathy with tubular acidosis was observed during attacks in 3 patients with CPT I deficiency (Bergman et al 1994; Falik-Borenstein et al 1992). Transient functional renal failure during acute attacks was observed in 13 patients. One patient with CPT II deficiency presented in the neonatal period with a transient salt-losing syndrome (personal unpublished observation.)

Miscellaneous presentations

In addition to the preceding well-known clinical pictures, a few other symptoms have been observed. Three patients with carnitine uptake deficiency displayed chronic anaemia, which was fully corrected after carnitine supplementation. Hypoparathyroidism has been reported in LCHAD and trifunctional enzyme deficiencies (Dionisi-Vici et al 1996; Tyni et al 1997). Stridor has been observed in a patient with riboflavin-responsive MAD (Sperl et al 1997). Acute fatty liver in pregnancy and HELLP syndrome (not observed in our series) have been described by several authors in mothers with a fetus affected with LCHAD deficiency (Innes et al 1997) and CPT I deficiency (Greenberg et al 1997). Although not elucidated, the EPEMA syndrome (encephalopathy, petechiae, acrocyanosis, recurrent metabolic crises, ethylmalonic aciduria) is possibly related to an inherited disorder of fatty acid oxidation (Burlina et al 1994; Garcia-Silva et al 1997). Finally, we must emphasize that many FAO disorders can remain asymptomatic for a very long time (Miyajima et al 1997; Smelt et al 1998; Vianey-Saban et al 1998), and even for life as demonstrated in adult MCAD individuals bearing the common homozygote mutation at the codon 985. This complete discrepancy between phenotype and genotype emphasizes the important role of environmental factors involved in acute decompensations in FAO disorders.

DIAGNOSTIC APPROACH TO FAO DISORDERS

In general, the best functional tests are performed by nature during an acute metabolic stress caused by an acute infection, inadvertant fasting or consumption of a nutrient for which a metabolic intolerance exists. If symptoms arise, blood and urine should be collected and stored in the correct way for performance of the endocrine and metabolic screening assays (Fernandes and Saudubray 1995; Saudubray and Charpentier 1995). However, investigation of FAO disorders has recently been radically simplified by investigating plasma acylcarnitine profiles by FAB-MS/MS or

electrospray MS/MS. This highly sophisticated method can detect or at least strongly suggest most FAO disorders from simple blood spots collected on a Guthrie card (Millington et al 1990, 1992; Rashed et al 1995; Schmidt-Sommerfeld et al 1992; Van Hove et al 1993). Using this methodology on Guthrie cards collected at birth, we retrospectively diagnosed CPT II and VLCAD deficiencies in two patients who died early in infancy from sudden infant death syndrome (Brivet et al 1996). Beside this very efficient technique, the most classical and convenient metabolic investigations for the diagnosis of FAO disorders are the determination of urinary organic acid profiles. These can give highly specific patterns (mostly in MAD, MCAD and HMG-CoA lyase deficiencies), suggestive but non-specific patterns (saturated and unsaturated medium and long-chain dicarboxylic acids with the hydroxylated derivatives in MCAD, LCHAD, trifunctional enzyme, VLCAD and MAD deficiencies), or a normal pattern which does not allow the exclusion a FAO disorder. Plasma and urine free and total carnitine concentrations can give important indications; in carnitine transport defects, plasma carnitine levels are severely decreased, contrasting with persistent carnitine excretion (Brivet 1999; Stanley et al 1991). In CPT I deficiency, total carnitine levels are increased (Stanley et al 1992). In all other defects, total carnitine levels are reduced to 25–50% of normal ('secondary' carnitine deficiency) but can also be close to normal.

If no material is collected at the time of acute attack, or if the results are incomplete or ambiguous, a function test that challenges the metabolic pathway may provide a tentative diagnosis. Unless there is a very strong clinical suspicion or in urgent situations, we always attempt such a challenge test, rather than 'blindly' performing *in vitro* fatty acid oxidation studies on lymphocytes or fibroblasts, which can be done in only a few laboratories and are time-consuming and expensive. When performing such a function test, it is very important to adhere to a strictly defined protocol to obtain the maximum diagnostic information and minimize the risk of metabolic complications. This functional test must be performed only when the patient is in good health and in a good nutritional state, when there is no basal disturbance of organic acids and acylcarnitine profile, and after an overnight short physiological fast (8 h). The phenylpropionic acid loading test (20 mg by mouth) is well tolerated and easy to perform. It is very convenient for diagnosing MCAD deficiency and some cases of LCHAD deficiency (Rumsby et al 1986). The medium-chain triglyceride loading test is generally not useful: it is normal in long-chain fatty acid oxidation defects but is difficult to interpret and possibly dangerous in MCAD and MAD deficiencies (Pollitt 1989). The long-chain triglyceride loading test, using unsaturated long-chain fatty acids such as sunflower oil (1.5 g/kg by mouth), screens the overall hepatic fatty acid oxidation pathway from cellular uptake of fatty acids to ketone body production. In our experience, it detects all defects in long-chain fatty acid oxidation and MAD in which plasma ketone bodies remain inadequately low after the load (Demaugre et al 1991; Parini et al 1991; Poll-The et al 1988). The response is not significantly disturbed in MCAD deficiency. When the long-chain fatty acid load is not significantly disturbed, a controlled fast under close medical supervision may be used as a diagnostic investigation and as an aid to giving therapeutic recommendations to the patient. Of course, this test has to be done under

very strict medical supervision. An inadequate ketogenic response with a high free fatty acid/ketone bodies ratio is strongly suggestive of a long-chain fatty acid oxidation defect (Bonnefont et al 1990). Finally, inherited defects of FAO can be diagnosed by *in vitro* testing using fresh circulating lymphocytes or intact cultured fibroblasts to oxidize individual fatty acids. So far all the described defects involving liver have been expressed in these cells (Saudubray et al 1982; Brivet et al 1995; Rhead 1990; Vianey et al 1987). An elegant and very efficient method is to measure the acylcarnitine profile after incubating cultured fibroblasts with labelled fatty acids (Nada et al 1995).

TREATMENT

As soon as a FAO disorder has been suspected, the most important goal is to provide sufficient glucose to prevent adipose tissue lipolysis. This is particularly true in the neonatal period and in acute metabolic attacks. Delay may result in sudden death, heart beat disorders, collapse, or permanent brain damage. This goal can be achieved by using intravenous solutions of 10% glucose rather than the usual 5%, infused at rates of 10–12 mg/kg per min or greater to maintain high to normal levels of plasma glucose above 5 mmol/L. Resolution of coma may not be immediate because of the toxic effects of fatty acids, but may take 2–4 h in mildly ill patients or as long as 1–2 days in severely ill patients. This infusion is difficult to perform in a peripheral vein. A central line catheter should be installed and later a portacath catheter for easy access in case of emergency. The oral route through a nasogastric drip using a 10–15% glucose polymer solution can also be used, if there is no vomiting and no diarrhoea, alone or with an intravenous infusion. L-Carnitine therapy is of course mandatory and life-saving in carnitine transport defects (100–200 mg/kg per day by i.v. route in emergency, then delivered orally 3–4 times a day). Carnitine therapy in those disorders of FAO that are associated with secondary carnitine deficiency has long remained controversial because of a theoretical risk of an acute accumulation of long-chain acylcarnitines, which were found arrhythmogenic in experimental situations (Corr et al 1989). However, recent clinical reports now strongly support carnitine administration in such circumstances; it is very well tolerated and helpful probably in lowering the accumulation of acyl-CoA and restoring the CoA pool in the mitochondria. Although only very few riboflavin-responsive MAD patients have been reported, it is mandatory to systematically try this therapy in such a disorder (Carroll et al 1981; Green et al 1985; Roettger et al 1992).

Long-term dietary therapy is aimed at preventing any period of fasting that would require the use of fatty acids as a fuel. In some disorders, such as MCAD and CPT I, and in partial defects of other long-chain fatty acid oxidation disorders, this management is very easy. In the most severe forms of long-chain fatty acid defects, however (as in the severe forms of CPT II, translocase, VLCAD, MAD, trifunctional enzyme and LCHAD deficiencies), all conditions in which even very small persistent lipolysis results in the accumulation of long-chain acylcarnitines, it is necessary to completely eliminate fasting by the addition of continuous nocturnal intragastric

feeding. An alternative could be the use of uncooked corn starch at bed time as recommended in the treatment of glycogenosis types I and III, with amylase for the first year of life. It is also recommanded to restrict long-chain fat intake and to give a medium-chain triglyceride supplementation at a dose of 2–3 g/kg per day during infancy, falling to 1–1.25 g/kg per day after the first year.

In LCHAD deficiency, an oral DHA supplementation could be tried according to the preliminary reports previously mentioned (Harding et al 1998).

With these therapeutic efforts, the short-term evolution of these patients has considerably improved. However the long-term prognosis still remains very guarded. If we except carnitine uptake defects in which carnitine supplementation works perfectly well and hepatic CPT I, MCAD, and muscular forms of CPT II deficiencies in which the long-term prognosis seems to be reasonably good, the long-term follow-up of the severe neonatal forms of long-chain and generalized fatty acid oxidation disorders remains unknown. Many LCHAD patients develop desperate retinitis pigmentosa leading to severe amblyopia, peripheral neuropathy and recurrent episodes of aching muscle pain despite avoidance of recurrent hypoglycaemic episodes. All patients who display cardiomyopathy (except those affected with carnitine-responsive carnitine uptake deficiency) are permanently exposed to the risk of unexpected death despite therapy. Parents should be informed of this possibility. This emphasizes the need also to inform parents of the possibility of antenatal diagnosis.

NOTE ADDED IN PROOF

Since this review was submitted, a new inborn error of fatty acid oxidation has been reported by Odaib et al (Odaib AA, Shneider BL, Bennett MJ et al (1998) A defect in the transport of long-chain fatty acids associated with acute liver failure. *N Engl J Med* **339**: 1752–1757).

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