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REGULAR REVIEW

Medium chain acyl-CoA dehydrogenase deficiency

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Abstract

From 65 reported cases of medium chain acyl-CoA dehydrogenase deficiency, we found an average presenting age of 13·5 months and a mean age at death of 18·5 months. One quarter of patients died of a Reye-like syndrome and/or sudden infant death. In half the cases there had been at least one sibling death. Asymptomatic cases were not uncommon (12% of cases). The crises were generally induced by a prolonged fast and after a viral prodromal phase in three quarters of cases. The crises consisted of somnolence progressing to lethargy which could lead to coma. Vomiting was frequent (60% of cases). Seizures, which were found in 29% of cases, represented a bad prognosis. The physical examinations revealed frequently a variable and regressive anicteric hepatomegaly.

Blood and urine analysis revealed in most instances hypoglycaemia (96% of cases) with hypoketonuria and sometimes metabolic acidosis. Hepatic and muscular cytolytic enzymes were frequently raised, as were plasma ammonia, urea, and uric acid. Plasma total or free carnitine concentrations, especially non-fasting, were diminished in most cases. Plasma saturated medium chain fatty acids and particularly unsaturated *cis*-4-decenoate were on the other hand raised during the crises or during fasting. Urinary organic acid analysis revealed a characteristic profile of medium chain aciduria: C_6–C_{10} dicarboxylic acids, hydroxy acids, glycine conjugates, and carnitine conjugates. Oral loading tests with carnitine or phenylpropionate allow a precise diagnosis. The diagnosis is confirmed by specific assays in various tissues. Avoidance of prolonged fasting seems to be the mainstay of treatment.

Fatty acid oxidation plays an important part in maintaining energy homoeostasis during fasting. Deficiency of medium chain acyl-CoA dehydrogenase (M-CAD)[1] was recently recognised as the most common hereditary disease of hepatic fatty acid oxidation and one of the commonest inborn errors of metabolism.[2] The incidence is estimated at 1/20 000 newborn infants and more than 85 patients have now been reported, in 65 of whom the diagnosis has been confirmed enzymatically.[3] This enzymatic defect was first suspected in 1976[4] and was initially reported as 'hypoketotic hypoglycaemia with C_6–C_{10} dicarboxylic aciduria' related to fasting.[5–8] M-CAD deficiency has been reported in Reye-like syndromes.[9 10] It is also recognised in familial and recurrent Reye's syndrome,[11 12] particularly in the first two years of life. M-CAD deficiency has been demonstrated in some cases of sudden infant death syndrome (SIDS).[13–17] Disease entities previously reported as systemic carnitine deficiency[18 19] have been recently demonstrated to be cases of M-CAD deficiency.[20–22]

The specific diagnosis of M-CAD deficiency was initially made in patients with an acute onset of the disease[23]; although more difficult, the diagnosis is now made in asymptomatic children.[16] The diagnosis has been mainly based on plasma and urinary organic acid analysis by means of gas chromatography and mass spectrometry (GC-MS).[24] The outcome may be fatal in the absence of appropriate therapeutic management.

In this general survey of the published patients with M-CAD deficiency, we discuss the principal features of this recently recognised enzymatic defect.

Results and discussion

CLINICAL FEATURES (table 1)

The average age for the first presenting episode in M-CAD deficiency was 13·5 months and varied between 2 months and 4 years. There was an equal distribution between the sexes (27 males and 26 females). The mortality rate was one quarter of the studied cases. Roe *et al* find the mortality rate as high as 60% for a first episode between the ages of 15 and 26 months.[3] The mean age at death was 18·5 months. The Reye-like syndrome and/or SIDS were the causes of death. In half the families studied, one or more previous sibling deaths had occurred.

*Table 1 Clinical information in 65 M-CAD deficient patients**

		%	*Range (months)*
Patient's history			
Sex distribution (M/F)	27/26		
Mean age of first episode (months)	13·5		2–48
Mortality rate	14/53	26	
Reye-like syndrome and/or SIDS	12 11		
Mean age at death (months)	18·5		7–30
Previous sibling death	16/33	48	
Presenting symptoms and signs			
Somnolence, lethargy, or coma	57/57	100	
Viral prodrome	34/46	74	
Vomiting	28/47	60	
Seizures	14/48	29	
Hepatomegaly			
Frank	12/32	38	
Total	19/32	59	
Asymptomatic	8/65	12	

*Only information recorded for each patient is indicated. Four neonatal cases were not included.

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The main presenting symptom of M-CAD deficiency was somnolence in 100% of symptomatic cases, progressing to lethargy which could lead to coma. This symptom was induced by fasting for longer than 12 hours. A viral prodromal episode, comprising mainly digestive and respiratory symptoms, was found in three quarters of the cases studied. Vomiting was frequent (60%). Seizures, which were less frequent (30%), indicated a poorer prognosis: six deaths and two cases of epilepsy were noted among the 14 patients with seizures. Frank hepatomegaly was noted in 38% of cases. Asymptomatic cases were not uncommon (12%).

It is important to note the absence of any delay in psychomotor development and growth, and the absence of clinical myopathic manifestations in the heart and skeletal muscles, such as frequently encountered in long chain acyl-CoA dehydrogenase deficiency.[25] Previous acute crises and recurrences are frequent in M-CAD deficiency.[20 21]

Table 2 Plasma values at presentation in M-CAD deficient patients

Investigation	*No (%) with abnormal result*	*Range or value*	
		Patients	*Controls*
Glucose (mmol/l)	45/47 (96)	0·10–0·25	3·3–5·5
β-hydroxybutyrate ×glucose ($mmol^2/l$)	5/5 (100)	0·17–3·70	9–14[15]
Free fatty acid: β-hydroxybutyrate (fasting)	10/10 (100)	1·4–56	<1[27]
Carbon dioxide (mmol/l)			
Moderate acidosis	7/23 (30)	11–15	21–28
Mild acidosis	9/23 (39)	16–19	
SGOT (U/l)*	17/19 (90)	43–924	<40
SGPT (U/l)*		48–696	<40
Ammonia (μmol/l)			
Moderate hyperammonaemia	9/18 (50)	>100	<60
Mild hyperammonaemia	5/18 (28)	>60	
Uric acid (μmol/l)	7/7 (100)	565–1428	<450
Urea (mmol/l)	8/9 (89)	7–28	<6·5
Lactate dehydrogenase (U/l)	3/3 (100)	503–1260	<250

*SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SGOT and/or SGPT were measured.

Table 3 Concentrations of plasma carnitine and medium chain fatty acids in M-CAD deficiency

	No (%) with abnormal result	*Range or value*	
		Patients	*Controls**
Remission, fed state			
Carnitine (μmol/l)†	21/22 (96)		
Total		7–36	40–60
Free		3–24	42±8
Acute, fasting state‡			
Carnitine (μmol/l)	10/13 (77)		
Acylcarnitine:free carnitine ratio	7/8 (88)	≥0·5	<0·5
Octanoate (C_8, μmol/l)	18/18 (100)	8–394	ND
Decanoate (C_{10}, (μmol/l)	14/16 (80)	7–96	ND
Cis-4-decenoate (μmol/l)	15/15 (100)	3–168	ND

*Reference values.[1 23]
†Other references indicate: total carnitine 5–23 μmol/l in nine patients,[21] free carnitine 1–24 μmol/l in 15 patients.[26]
‡Including fasting tests.
ND, not detected.

Table 4 Main urinary metabolites in M-CAD deficiency

	No (%) with abnormal results	*Range (μmol/mmol creatinine)*	*Controls**	
			Fasting	*Ketosis*
Ketones (ketosticks)	18/21 (85)	Negative to +	≥++	
↑ Dicarboxylic acids (in acute state)				
Adipate C_6	41/43 (95)	+ to ≥50	<15	<300
Suberate C_8	41/42 (98)	+ to ≥40	<13	<50
Sebacate C_{10}	37/39 (95)	+ to ≥30	<11	<18
↑ Hydroxy acids				
5-Hydroxyhexanoate C_6	20/21 (95)	+ to ≥50	<10	
↑ Glycine conjugates (in acute state or remission)				
Hexanoylglycine	25/28 (90)	+ to ≥10	<1	<1
Suberylglycine	27/27 (100)	+ to ≥9	<2	<2
Phenylpropionylglycine†	24/25 (96)	0·6–98	<0·6	
↑ Carnitine conjugates				
Octanoylcarnitine‡	26/26 (100)	+ to ≥4	<1	

*Age: 1 day–15 years (n=70) receiving regular diet with no supplementary medium chain triglycerides.[24]
†21 Patients accurately identified with stable-isotope dilution assay.[28]
‡12 Patients exclusively identified by FAB-MS.[30]

PLASMA FEATURES (table 2)

During the crises, hypoglycaemia was constantly present (96%). Plasma β-hydroxybutyrate was disproportionately low given the hypoglycaemia, thus defining a hypoketotic hypoglycaemic state. M-CAD deficiency was characterised by a deficient ketogenesis, demonstrated by an abnormal (high) free fatty acids:ketone bodies ratio during fasting in all analysed cases. Moderate metabolic acidosis was found in 30% of the studied cases. Plasma transaminases concentrations were almost always raised. This increase has sometimes been progressive with the appearance of a secondary hepatomegaly.[11] There was moderate hyperammonaemia in half the cases. Plasma uric acid, urea, lactate dehydrogenase, and creatine kinase were also frequently at high concentrations during the crises. The prothrombin time was sometimes diminished (3/7) and plasma bilirubin was normal.

M-CAD deficiency is generally characterised by secondary carnitine deficiency and abnormal high acylcarnitine:free carnitine ratios (table 3).[26] In the fed state, free or total carnitine were almost always at low concentrations in the plasma, thus defining a permanent hypocarnitinaemic state. In acute crises, or in fasting tests, hypocarnitinaemia was found in 77% of cases, less frequently than in the fed remission state. In six untreated M-CAD deficient patients[3] tissue carnitine concentrations in muscle and liver are about 25% of normal. The acylcarnitine:free carnitine ratio was abnormal in seven out of eight cases during the crises or fasting tests. This parameter seems to be the best indicator of symptomatic M-CAD deficiency. There was a constant high concentration of saturated octanoate and especially unsaturated *cis*-4-decenoate in plasma during crises or fasting tests. *Cis*-4-decenoate detection is considered to be pathognomonic of M-CAD deficiency and is not influenced by dietary supplementation with medium chain triglycerides.[27]

URINARY FEATURES (table 4)

Hypoketonuria was found in 85% of cases. The analysis of urinary organic acids by GC-MS during the acute episodes revealed a C_6–C_{10} dicarboxylic aciduria (C_6 adipate, C_8 suberate, C_{10} sebacate) and a monocarboxylic (omega-1) hydroxylated aciduria (5-hydroxyhexanoate). These metabolites are produced by the deviation of fatty acid oxidative metabolism towards alternative microsomal pathways. This urinary profile is characteristic of M-CAD deficiency.[24]

Specific metabolites of M-CAD deficiency (especially hexanoylglycine, suberylglycine, and phenylpropionylglycine) are found and quantified during the crises and remissions using recent sensitive assays, especially the stable

isotope dilution measurement.[28] This assay allows the differential diagnosis between M-CAD deficient infants and normal infants receiving formulas supplemented with medium chain triglycerides.[29] Urinary medium chain acylcarnitines, especially octanoylcarnitine, are also found in the analysed cases, mainly using fast atom bombardment mass spectrometry (FAB-MS).[30]

PATHOLOGICAL FEATURES

Panlobular microvesicular macrovesicular hepatic steatosis was generally present in M-CAD deficient patients during the acute crises. Ultrastructural analysis of hepatic mitochondria may differentiate M-CAD deficiency from idiopathic Reye's syndrome, mainly by a condensed matrix appearance with widening of the intracristal spaces.[21]

IN VIVO DYNAMIC TESTS

Fasting tests revealed M-CAD deficiency by the detection of specific plasma and urinary metabolites. These tests are potentially dangerous, as shown by eight out of 16 cases where serious clinical manifestations were provoked, including lethargy, one case of coma after only 12 hours of fasting[31] and one case of death.[4] These clinical manifestations are not necessarily correlated with hypoglycaemia.[20 32]

Oral loading tests with lipid and medium chain triglycerides were also potentially dangerous, inducing neurological deterioration in two cases,[8 11] and an aggravation of hepatomegaly in one case.[10] Oral loading with carnitine (100 mg/kg) helped in establishing the diagnosis of M-CAD deficiency, with no risk to the patients, by the detection of urinary octanoylcarnitine.[16 30]

The phenylpropionic acid oral loading test is based on the fact that phenylpropionate is oxidised by the M-CAD enzyme to benzoic acid, which is then excreted in the urine as hippuric acid.[33] After oral loading with phenylpropionate (25 mg/kg), control subjects and parents excreted only hippurate, whereas the urinary metabolites of M-CAD deficient patients consisted of approximately one third phenylpropionylglycine and two thirds hippurate.[34 35]

IN VITRO TESTS

Enzymatic diagnoses were first performed by a global assay of fatty acid oxidation in intact cultured fibroblasts.[36 37] This procedure consists of measuring liberated carbon dioxide from 1-^{14}C fatty acid substrates of varying chain length (C_{16} palmitate, C_8 octanoate, C_4 butyrate) in order to determine the specific enzymatic activity for the three acyl-CoA dehydrogenases (long, medium, and short chain ACD) involved in mitochondrial β-oxidation. In M-CAD deficiency, the mean enzymatic activity with 1-^{14}C octanoate as substrate varies between 10% and 29% of normal (n=21).[38]

The specific enzymatic dosages[3] have been obtained in hepatocytes, fibroblasts, peripheral mononuclear leucocytes, cardiac myocytes, skeletal myocytes, and amniocytes. In M-CAD deficiency, the specific enzyme activity measured with octanoyl-CoA as substrate is between 3% and 10% (n=40) with a mean of 6%.[3]

The molecular studies confirmed a single prevalent point mutation consisting of lysine to glutamate substitution on chromosome 1.[39] This point mutation is present in more than 90% of the alleles[40] and could represent a highly distinctive feature of M-CAD deficiency.

POSTMORTEM RECOGNITION

M-CAD deficiency should be suspected after unexpected death in infancy and death from Reye's syndrome. Specific postmortem diagnosis may be made by the finding of raised concentrations of plasma *cis*-4-decenoate[27] and the detection of urinary or hepatic octanoylcarnitine by FAB-MS.[41] Specific enzymatic assays in various frozen tissues led to the diagnosis of M-CAD deficiency in SIDS.[42]

Retrospective studies estimate the frequency of M-CAD deficiency in the SIDS population at about 1–2% in England[14 17] and possibly also in France (1/110) (P Divry, personal communication).

PRENATAL DIAGNOSIS

Prenatal diagnosis has already been achieved in a sibling of a SIDS case with M-CAD deficiency, and later confirmed in the neonatal period.[43]

TREATMENT

During the crises, symptomatic treatment is necessary to overcome the hypoglycaemia, cerebral oedema, seizures, or metabolic acidosis. The mainstay of treatment of M-CAD deficiency is the prevention of an acute episode by avoiding prolonged fasting periods and by providing glucose supplementation.[2 32] A low fat diet is not necessarily recommended.[12] L-Carnitine administration (100 mg/kg/day) is considered to be beneficial,[30 31] but this is contested by some authors who did not find an improvement in fasting—induced ketogenesis after L-carnitine supplementation.[32 44] Carnitine seems to be important in the elimination of potentially toxic metabolites accumulating after enzymatic block. This is recently confirmed by the finding of a greater excretion of medium chain acylcarnitines after L-carnitine administration.[45]

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