MADD or drunk? Adults have inborn errors too

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Severe genetic enzyme deficiencies cause acute illness in early life and paediatricians are familiar with their presentation. Milder defects may present in adults under conditions of abnormal metabolic stress. Because of their rarity they may be missed.

DISCUSSION

MADD is a rare autosomal recessive disorder with a deficiency of electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase (ETF-QO) (Frerman and Goodman, 1995). These are proteins with a flavin co-factor derived from riboflavin. They work in tandem to carry electrons from at least nine dehydrogenases into the mitochondrial respiratory chain (*Figure 1*). Their deficiency has widespread repercussions with impaired β-oxidation of long chain fatty acids, ketone production, gluconeogenesis, ammonia detoxification and catabolism of choline and amino acids. A host of organic acid intermediates accumulates. Some are conjugated with carnitine forming acylcarnitines detectable in blood and urine. This depletes body carnitine reserves.

Clinically, there is intolerance of fasting with risk of hypoketotic, hypoglycaemic coma, metabolic acidosis and fatty infiltration of the liver, renal tubules, myocardium and skeletal muscle. The most severe cases have a fulminating neonatal illness and die within days. Milder cases have recurrent hypoglycaemia with encephalopathy and coma, cardiomyopathy and progressive proximal myopathy. Most die in childhood. There are only two other reports of MADD presenting with metabolic crises in adults. One patient died at 19 years (Bell et al, 1990). The other became comatose after vomiting when 12 weeks pregnant but recovered (Dusheiko et al, 1979). Both patients had ETF-QO deficiency, but with relatively high residual enzyme activity compared with severely affected babies (Loehr et al, 1990).

From the fibroblast studies, our patient probably has a mild deficiency too. Other adults have presented non-acutely with progressive lipid storage proximal myopathy (Mongini et al, 1992). Treatment is with a high carbohydrate, low fat, low protein diet with carnitine supplements. Riboflavin is also given since a minority of patients have responded to this treatment (Harpey et al, 1983; Frerman and

CASE REPORT

A 31-year-old woman returned from holiday in Spain after drinking very heavily. Next day, she was admitted with a 12-hour history of vomiting, diffuse abdominal pain and increasing lethargy. Her only previous medical history was a paroxetine overdose 4 weeks earlier. She was drowsy, apyrexial, uncooperative and appeared drunk. Abdominal tenderness was attributed to pelvic inflammatory disease. Blood pressure was 120/80 mmHg, pulse 80/min and regular, and she had a systolic murmur. Plasma glucose was 3.9 mmol/litre, urea 9.5 mmol/litre, creatinine 103 μmol/litre, alanine aminotransferase 86 IU/litre (reference value (RV) <35 IU/litre) and amylase 156 IU/L (RV <100 IU/litre). Five per cent dextrose was infused intravenously for 12 hours, after which she was awake and cooperative. When discontinued she became increasingly drowsy and after 8 hours was unrousable, Glasgow coma scale (GCS) 7/15, with an unrecordably low blood glucose. Amylase was 101 IU/litre. She was resuscitated with intravenous dextrose and oxygen and improved initially (GCS 11/15). Arterial pH was 7.09, bicarbonate 9.1 mmol/litre, partial pressure of oxygen 24.98 kPa, partial pressure of carbon dioxide 4.2 kPa and lactate 0.7 mmol/litre (RV <2.8 mmol/litre). Urine pH was 5.0 and ketones >1.5 mmol/litre. An electrocardiogram showed sinus tachycardia and cardiac echocardiogram, a hyperdynamic left ventricle and prolapsing mitral valve. She became agitated, hypotensive (systolic pressure 70 mmHg), shut-down peripherally and anuric. Despite intravenous bicarbonate, she remained severely acidotic with normal lactate. Differential diagnoses were drug overdose, ethylene glycol or methanol ingestion, alcoholic ketoacidosis or septicaemia. Treatment included haemofiltration, intravenous inotropes, glucose, bicarbonate, metronidazole, cefuroxime and ethanol (discontinued after negative toxicology results). Her condition was parlous over the next 48 hours.

To look for an explanation for her metabolic acidosis, urine was sent for urgent organic acid analysis. The profile was grossly abnormal and consistent with the inherited disorder MADD (multiple acyl-CoA dehydrogenase deficiency or glutaric aciduria type II (McKusick 23168)). Blood was collected for acylcarnitine analysis and a skin biopsy for fibroblast culture for enzyme studies. Treatment was commenced with intravenous carnitine (100 mg/kg per 24 hours) and riboflavin (100 mg 8-hourly). Her condition improved gradually. Recovery was complicated by pneumonia, adult respiratory distress syndrome and *Clostridium difficile* diarrhoea. She was discharged after 5 weeks on a high carbohydrate, low fat, low protein diet with oral carnitine and riboflavin supplements. She had normal renal function, but weight loss and proximal muscle weakness with a normal creatine kinase (97 IU/litre; RV 24–173 IU/litre). This resolved after 12 weeks. She remains well 1 year later.

Acylcarnitine profiles, analysed acutely and during recovery, were abnormal and consistent with MADD, and urinary organic acid abnormalities persisted. Screening of fibroblasts for fatty acid β-oxidation (tritium release assay) showed reduced activity consistent with mild MADD. There was no evidence in vitro that the defect was responsive to riboflavin.

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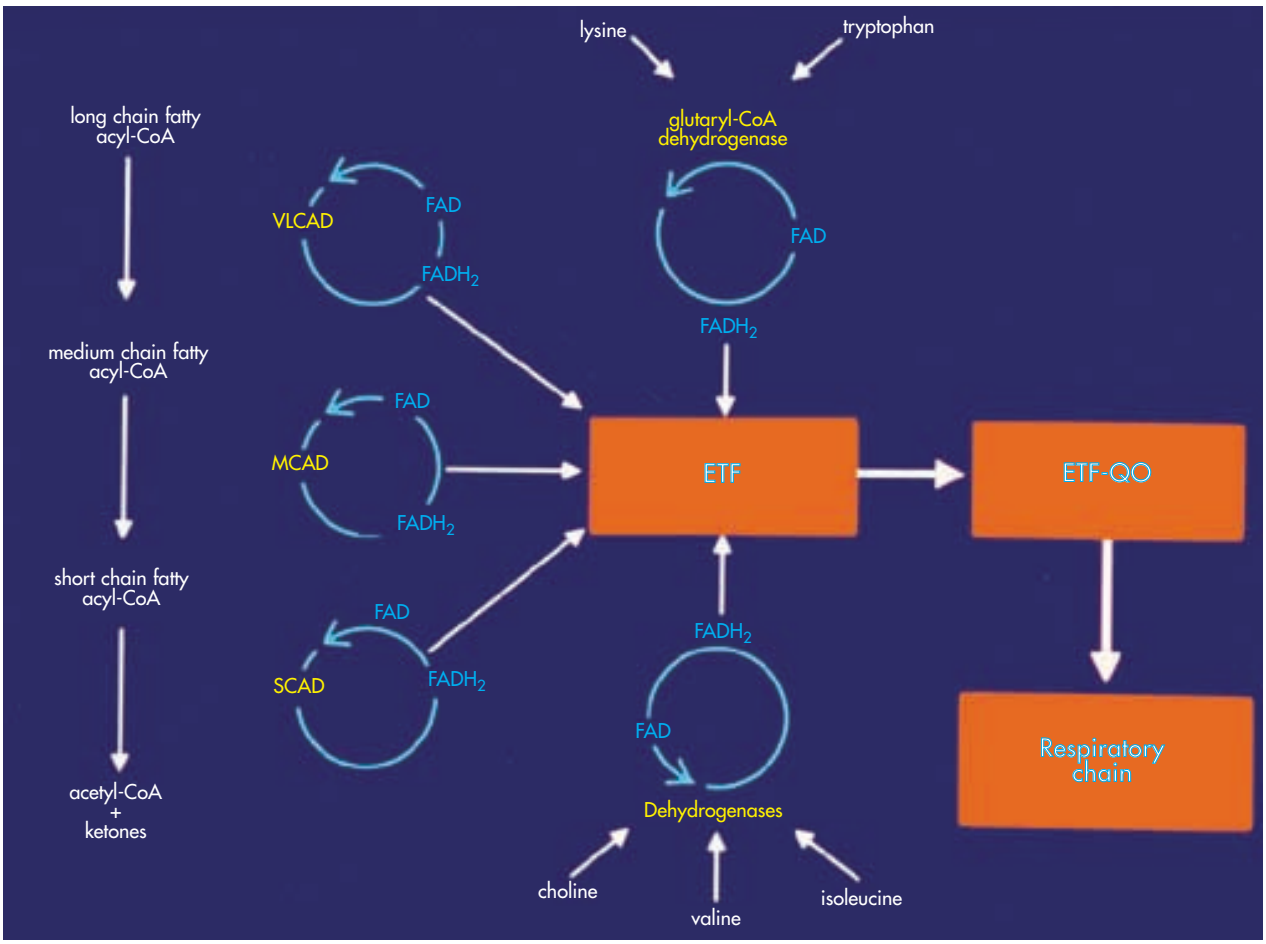

Figure 1. Electron transfer protein (ETF) and ETF-ubiquinone oxidoreductase (ETF-QO) carry electrons from 9 dehydrogenases to the respiratory chain. VLCAD, MCAD, SCAD = very long chain, medium chain and short chain acyl-CoA dehydrogenase; FAD = flavin adenine dinucleotide.

Goodman, 1995). The only report of pregnancy in MADD indicates that mothers may be at risk and their babies likely to die in infancy if the defect is not riboflavin-responsive (Harpey et al, 1983).

CONCLUSIONS

As well as MADD, other genetic defects of metabolism also, rarely, present acutely in adults, including defects of fat oxidation, the urea cycle (Arn et al, 1990) and the mitochondrial respiratory chain (Chinnery and Turnbull, 1997). They may not be recognized. Clues are unexplained encephalopathy, hypoglycaemia, severe metabolic acidosis or rhabdomyolysis, perhaps precipitated by fasting, strenuous exercise, pregnancy or sodium valproate. Specialist advice should be sought early since urgent investigation is imperative. **HM**

Fibroblast enzyme studies were undertaken by Dr Simon Olpin, Sheffield Children's Hospital, and acylcarnitine analyses by Dr Andrew Johnson and Professor Peter Clayton, Institute of Child Health, London.

KEY POINTS

- Metabolic defects may present acutely in adult life.
- Alcohol and starvation may precipitate metabolic crises.
- In unexplained encephalopathy consult a metabolic physician early, and check acid/base status, ammonia, lactate, acylcarnitines, urine organic acids. Specialist laboratories will help.

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