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REVIEW

Adult presentations of medium-chain acyl-CoA dehydrogenase deficiency (MCADD)

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Summary Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is an autosomal recessive disorder of mitochondrial fatty acid oxidation which is usually diagnosed in infancy or through neonatal screening. In the absence of population screening, adults with undiagnosed MCADD can be expected. This review discusses 14 cases that were identified during adulthood. The mortality of infantile patients is approximately 25% whereas in this adult case series it was shown it to be 50% in acutely presenting patients and 29% in total. Therefore, undiagnosed individuals are at risk of sudden fatal metabolic decompensation with high mortality. This review illustrates the need to consider the possibility of a fatty acid oxidation defect in an adult who presents with unexplained sudden clinical deterioration, particularly if precipitated by fasting or alcohol consumption. A history of unexplained sibling death may also raise the index of suspicion. There also needs to be appropriate clinical support for those patients identified clinically or as a result of family studies (sibling or parent).

Abbreviations

AFLP	acute fatty liver of pregnancy
CPT I	carnitine palmitoyltransferase I
CPT II	carnitine palmitoyltransferase II
HELLP	syndrome of haemolysis, elevated liver enzymes, and low platelets
LCHAD	long-chain hydroxy-CoA dehydrogenase deficiency
MADD	multiple acyl-CoA dehydrogenase deficiency
MCADD	medium chain acyl-CoA dehydrogenase deficiency
MTP	mitochondrial trifunctional protein deficiency
VLCAD	very long chain acyl-CoA dehydrogenase deficiency
VPA	valproate

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Introduction

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is an autosomal recessive disorder of mitochondrial fatty acid oxidation (Roe and Coates 1995). Diagnosis is usually in infancy after an acute presenting illness or death (Roe and Coates 1995). Its estimated prevalence in the UK is 1.4 in 10 000 (UKCSNS-MCADD 2008). It is included in a number of neonatal screening programmes around the world. A UK-wide neonatal screening programme for MCADD was introduced in April 2009. From comparison of expected prevalence from calculated gene frequencies with numbers of known patients it was concluded that many cases remain undetected (Seddon et al. 1995). In the absence of screening, diagnosis of MCADD is usually in infancy or early childhood with acute metabolic decompensation precipitated by intercurrent illness and/or reduced food intake.

Mortality in the infantile cases is approximately 25% (Derks et al. 2006; Touma and Charpentier 1992; Wilcken et al. 1994). However it is possible for some

of these undiagnosed cases to be detected during adult life through clinical presentation or as a result of a family member being identified. This review aims to discuss those cases where the patient was identified as aged more than 15 years old.

Methods

Literature searches for published adult cases of MCADD were performed on PubMed (http://www.pubmed.gov) using keywords MCADD and sudden death in adulthood and browsing references of all resulting papers. Searches were performed from the date of the first described case of MCADD in 1983 to the present day (Stanley et al. 1983). The corresponding authors of those papers in which patients were described as living were contacted with a request for an update on clinical history, progression, further episodes or death.

Cases

A literature search revealed 14 previously reported cases of adults who were first identified as having the condition during adulthood. Table 1 summarizes the presentations of adult cases. There were 6 male patients and 8 female patients with an age range of 16–45 years at time of presentation. Five asymptomatic subjects were identified through family studies as a result of offspring or close relatives being identified in infancy (cases 10–14). A further individual was identified as a result of a sibling death in adulthood (Losty et al. 2001). There were also an additional two individuals mentioned by Derks and colleagues (2006) in their paper discussing natural history and outcome who were symptomatic during infancy but only diagnosed in adulthood. The remainder of the cases presented clinically following metabolic stress and are described below. Updates were received regarding 4 out of 10 live individuals described in Table 1 and are either discussed in the text or described in the table. The case of Heptinstall and colleagues (1995) was lost to follow-up.

Case 1 (Ruitenbeek et al. 1995)

The patient, a 30-year-old man presented with acute encephalopathy and rhabdomyolysis following a bout of strenuous exercise in the cold without adequate nutrition. He had headaches, nausea and vomiting. On admission his creatine kinase was raised as expected but his glucose was normal. He had had one previous similar episode a year earlier when he had reduced food intake. Clinical examination revealed signs of left ventricular hypertrophy and re-polarization disturbances. Total and free carnitine status was low but resolved with carnitine supplementation, which was stopped after 9 months.

Case 2 (Wilhelm 2006)

The patient, a 19-year-old woman, presented with lethargy, disorientation and vomiting following ingestion of alcohol and marijuana. Within 24 h of her onset of illness she died from a cardiopulmonary arrest. She was not hypoglycaemic and ammonia and carnitine were not measured. She had had one previous episode with a Reye-like presentation at the age of 2 years. She was not taking any medication but was said to be allergic to aspirin.

Case 3 (Mayell et al. 2007)

The patient, a 16-year-old girl, presented similarly to patient 2 following an alcohol binge with starvation and vomiting. She presented clinically with acute encephalopathy and her condition deteriorated rapidly to coma. She was not hypoglycaemic, though she did have a slightly raised ammonia at 75 μmol/L (reference range <40 μmol/L). She also exhibited some rhabdomyolysis, which was not thought to be attributed to the alcohol ingestion. She had cardiovascular problems early in her admission, with left ventricular hypertrophy and global ventricular impairment, periods of bradycardia and ventricular ectopics. Free carnitine measured at the time was 12 μmol/L (reference range 15–53 μmol/L). Her only medical history of note was asthma and a febrile convulsion at 2 years of age.

Case 4 (Losty et al. 2001)

The patient, a 23-year-old woman, presented with severe vomiting, abdominal pain and encephalopathy following a heavy bout of drinking. She subsequently died from cardiac arrest. She had been admitted several times over a four-year period with similar symptoms, sometimes following ingestion of alcohol. Hypoglycaemia was recorded on only one occasion.

Case 5 (Feillet et al. 2003)

The patient, a 33-year-old man with a history of chronic alcoholism, presented with lethargy, vomiting and headaches. On admission he was hypoglycaemic (2.4 mmol/L) and had a raised ammonia (390 μmol/L,

controls <50 μmol/L). He became more encephalopathic and developed cardiovascular problems including ventricular tachycardia and ventricular fibrillations causing a cardiac arrest, which he survived. During his stay in intensive care he also developed rhabdomyolysis. Carnitine levels were not reported but he was treated with carnitine supplementation.

Case 6 (Raymond et al. 1999)

The patient, a 45-year-old woman, presented clinically on the third day postoperatively following a successful left colon resection to remove an adenocarcinoma. She had nausea and was mildly hypoglycaemic. She became more encephalopathic as the day went on and died from respiratory arrest. Postmortem carnitine studies showed a low free carnitine of 13 μmol/L (reference range 24–63 μmol/L). She had no previous clinical history of note but had lost approximately five pounds in weight prior to surgery. There were no similar episodes in her history, though it was noted that she had nausea and discomfort following an overnight fast for another colonoscopy.

Case 7 (Boles et al. 1996)

The patient, a 16-year-old girl, presented with a one-day history nausea and vomiting following an upper respiratory tract infection. She was found unresponsive at home and transferred to hospital but died shortly after. She was hypoglycaemic with significantly raised ammonia (714 μmol/L, normal 10–64 μmol/L). Similar episodes of altered consciousness following vomiting were described by the parents.

Case 8 (Santos et al. 2007)

The patient, 29-year-old pregnant woman, presented at 39 weeks' gestation with suspected acute fatty liver of pregnancy (AFLP). Following delivery of a healthy boy, cord blood was obtained for a study being performed and exhibited a high octanoylcarnitine level. Further investigations identified that the mother was the proband, with her newborn being unaffected. She described no similar episodes of hypoglycaemia though she had lost a sibling aged 8 months from cot death following gastroenteritis.

Discussion

MCADD is a candidate disease for neonatal screening and is already included in a number of schemes in Europe, the Americas, Africa and the Asia Pacific region (Bodamer et al. 2007; Borrajo 2007; Padilla and Therrell 2007; Saadallah and Rashed 2007; Therrell and Adams 2007). Newborn screening for MCADD has been introduced in England as a result of the successful outcome of the pilot screening performed by the UK Collaborative Study of Newborn Screening for MCADD (UKCSNS_MCADD 2008).

In the absence of neonatal screening, the majority of cases are detected clinically during infancy with hypoketotic hypoglycaemia. A study of 120 patients found the average age of onset as 12 months (Lafolla et al. 1994). These patients presented with variety of clinical symptoms (Table 2), with the majority (95%) requiring emergency admission. A comparison of the symptoms exhibited by the infant and adult cases was performed. The percentages of the infant cases in Table 2 were compared against the adult cases using a test for differences between proportions. There was a significant different in a number of symptoms exhibited by patients including lethargy, encephalopathy, hepatomegaly, seizure and apnoea. The majority of symptoms were precipitated by infection and or reduced intake of food, with a majority of both infant and adult patients presenting with vomiting. An accumulation of free fatty acids and impaired gluconeogenesis resulted in hypoketotic hypoglycaemia. Encephalopathy was observed in over 50% of infantile cases (Lafolla et al. 1994; Touma and Charpentier 1992) and is probably due to a number of mechanisms including an accumulation of toxic metabolites such as octanoic acid (Kim et al. 1990), decenoic acid and *cis*-4-decenoic acid (Schuck et al. 2007).The expression of enzymes involved in β-oxidation by immunohistochemistry suggested that dysfunction of the blood—brain barrier may contribute to the encephalopathy (Tyni et al. 2004) through marked lipid peroxidation by *cis*-4-decenoic acid, possibly through free-radical synthesis (Schuck et al. 2007). Cardiac symptoms, especially arrhythmia, are not normally described in infantile cases (Bergmann et al. 2001; Bonnet et al. 1999) but were evident in a number of the acute adult cases.

The symptoms exhibited by the acute adult cases were precipitated by a number of different factors (Table 1). All the factors described are known to stress individuals metabolically and particularly the mitochondrial fatty acid oxidation pathway (Wanders et al. 1999). Whereas the infantile clinical presentations are acute, the adult presentations may present as an acute on chronic situation. Only 50% of adults had a recorded episode of hypoglycaemia compared the majority of cases in infancy (96%; Touma and Charpentier et al. 1992). An important observation in the adult patients clinical

Table 1 Summary of adult MCADD cases

Case	Sex	Age at presentation	Precipitating factor	Significant clinical history	Outcome	Mutation	Reference
1	Male	30 years	Strenuous exercise without adequate food intake	One episode at 1 year old	Alive No update available	Homozygous for 985A>G	Ruitenbeek et al. (1995)
2	Female	19 years	Alcohol	Reye-likes illness at 2 months	Died from cardiopulmonary arrest Premortem bloods exhibited markedly elevated octanoylcarnitine. Postmortem analysis of liver showed macrovesicular steatosis	Compound heterozygous 985A>G/617G>T* *Mutation reported by Yang et al. (2000)	Wilhelm (2006)
3	Female	16 years	Alcohol binge and starvation	Febrile convulsion at 2 years	Alive No update available	Homozygous for 985A>G	Mayell et al. (2007)
4	Female	23 years	Alcohol	Several previous hospital admissions following drinking	Died from cardiac arrest	Homozygous for 985A>G	Losty et al. (2001)
5	Male	33 years	None of note, but history of heavy drinking	None	Alive No further episodes since initiating carnitine therapy	Homozygous for 985A>G	Feillet et al. (2003)
6	Female	45 years	Surgery	Nausea following preparation for colonoscopy	Died from respiratory arrest	Homozygous for 985A>G	Raymond et al. (1999)
7	Female	16 years	Viral illness and vomiting	Previous episodes of altered consciousness and vomiting	Death	Homozygous for 985A>G	Boles et al. (1996)
8	Female	29 years	Pregnancy	Weakness when fasting Unexplained cot death of sibling aged 8 months	Alive No update available.	Homozygous for 985A>G	Santos et al. (2007)
9	Male	44 years	Asymptomatic father of 3 affected children	None	Alive No update available	Not reported, though patient had significantly decreased octanoate oxidation on fibroblast studies	Duran et al. (1986)
10	Male	41 years	Asymptomatic father of 2 affected children. (Heptinstall case)	Chickenpox and rubella as child Always had a liking for sweet food Two experiences of anaesthesia	Alive No update available	Homozygous for 985A>G	Heptinstall et al. (1995)
11	Male	29 years	Asymptomatic sibling of Case 4	None	Alive No update available	Homozygous for 985A>G	Losty et al. (2001)
12	Male	29 years	Asymptomatic father of 1 affected child	Hypoglycaemic shock at 11 months after fasted period Has avoided fasting since	Alive Patient entirely well since diagnosis and treatment	Homozygous for 985A>G	Bodman et al. (2001)

13	Female	20 years	Pregnant and checked at 20 weeks due to sudden death of paternal cousin	None	Alive No update available	Compound heterozygous 985A>G/799G>A No biochemical diagnosis reported	Wang et al. (2002)
14	Female	34 years	Asymptomatic mother of 2 affected children	Coma following gastroenteritis and fever at 16 months Advised to avoid fasting and regular feeds during infection	Alive Without increased medical follow up had 3 uneventful pregnancies and deliveries	Homozygous for 985A>G	Derks et al. (2004)

histories was that 8 of the 14 patients had experienced one or more previous episodes of suspected metabolic crisis (Reye-like episode, hypoglycaemia). Two of the asymptomatic cases had even being advised to avoid fasting as a result of a hypoglycaemic episode in infancy (Bodman et al. 2001; Derks et al. 2004). One patient had lost a sibling due to unexplained cot death at 8 months of age (Santos et al. 2007). It is therefore imperative that a full clinical and family history is obtained from the patient or family members in order to ascertain any clues to the diagnosis. In the absence of hypoglycaemia, other mechanisms must be responsible for the clinical presentations in adults.

Alcohol

One-third of acute admissions of adult patients were precipitated by recent ingestion of alcohol (cases 2–5). In all cases alcohol intoxication resulted in vomiting, which may have caused a fasting state that could have further metabolically stressed these subjects (Table 2). Ethanol is metabolized in the liver and excess or chronic consumption may result in fatty liver (steatosis), which may cause more advanced pathology to develop including fibrosis, cirrhosis and hepatocellular carcinoma (Donohue 2007). At a molecular level, alcohol consumption activates the sterol regulatory element binding protein 1 (SREBP-1) which induces lipid biosynthesis genes. There is also a downregulation of peroxisome proliferator-activated receptor alpha (PPAR-α) which is associated with fatty acid oxidation and transport of fatty acids into the mitochondria (Donohue 2007). There is therefore an accumulation of fatty acids, some which are thought to be toxic.

Carnitine depletion

Five adult patients were found to have low free carnitine levels at time of presentation including two asymptomatic cases (Table 3). Treatment of the MCADD involves avoidance of fasting and supplementation of L-carnitine to replenish a deficiency due to accumulation of acyl-carnitines and an increased urinary loss (Longo et al. 2006; Wanders et al. 1999). An absence of carnitine would allow a build-up of toxic metabolites (Wanders et al. 1999), inhibiting mitochondrial fatty acid oxidation and possibly causing arrhythmias (Oliver 2006; Yamada et al. 1994). Kim and colleagues (1990) also showed that pre-treating rats with L-carnitine prior to exposure of octanoic acid resulted in little or no change in mitochondrial function in the choroid plexus, and this may be a mechanism for preventing encephalopathy caused by cerebral oedema. Deficiency of carnitine may also

Table 2 Signs and symptoms of acute presentation of MCADD

Symptom	Percentage of infant cases in Lafolla study	Percentage of infant cases in Touma and Charpentier study	Percentage of published adult cases	*p* value
Lethargy	84	100	37.5	0.003
Emesis	66	60	62.5	0.970
Encephalopathy	49	Not defined separately	62.5	0.014
Respiratory arrest	48	Not recorded	12.5	0.180
Hepatomegaly	44	59	0	0.0004
Seizures	43	29	0	0.004
Apnoea	37	Not recorded	0	0.039
Cardiac arrest	36	Not recorded	37.5	0.293
Sudden death	18	26	29	0.511
Rhabdomyolysis	Not recorded	Not recorded	37.5	

reduce the capacity for removal of the toxic metabolites (octanoic acid, decenoic acid and *cis*-4-decenoic acid) from the choroid plexus in brain and hence also causing encephalopathy (Kim et al. 1990; Schuck et al. 2007).

Valproate (VPA) has been associated with an induced carnitine deficiency by a number of mechanisms (Silva et al. 2008). Fatal liver failure has been reported in association with undiagnosed MCADD in a 9-year-old child started on valproate 4 months before death (Njolstad et al. 1997). None of the described patients were receiving VPA. However, is it possible that an undiagnosed patient may be become carnitine deficient owing to long-term VPA therapy and be more prone to a metabolic decompensation.

Cardiac symptoms

The first five cases had cardiac involvement in their acute presentation, with two dying from cardiac arrest. Derks and colleagues (2006) described 11 adult patients, identified in infancy, who were found on follow-up to have no cardiovascular abnormalities. The heart normally maintains its energy demands via myocardial fat and carbohydrate oxidation of circulating glucose, free fatty acids and triglycerides (Chess and Stanley 2008), although fatty acids are the main source (Wanders et al. 1999). On fasting there is an increase in the plasma pool of free fatty acids, which is taken up by the cardiac pool and oxidized. This inhibits glucose oxidation by inhibiting pyruvate dehydrogenase and results in increased myocardial triglycerides and glycogen stores (Chess and Stanley 2008). Chronic exposure to high plasma free fatty acids, as a consequence of type II diabetes mellitus, obesity or lack of exercise, will lead to increased uptake of free fatty acids into the cardiomyocytes, which may result in the production of toxic intermediates. In patients in whom there may be a deficiency in the β-oxidation of such substrates, it is possible that these intermediates will have undesired effects.

Bergmann and colleagues (2001) discussed the substrate availability for β-oxidation in patients with inherited deficiencies and showed that there was an expansion of the slow-turnover fatty acid pool due to deficient palmitate oxidation. There were accumulations of long-chain acyl-carnitines and intermediates that were suspected of being arrhythmogenic (Oliver 2006; Yamada et al. 1994). Bonnet and colleagues (1999) observed that there were no arrhythmias in patients with MCADD as the medium-chain fatty acids are not carried in the mitochondria by the carnitine—acylcarnitine shuttle. Therefore, another mechanism must be causing the cardiac arrhythmias. Patients with carnitine deficiency were compared with patients with

Table 3 Total and free carnitine levels in adult MCADD patients

Case (number refers to Table 1)	Total carnitine (μmol/L)	Quoted reference range (μmol/L)	Free carnitine (μmol/L)	Quoted reference range (μmol/L)	Reference
1	13–43	>25	6–38	>20	Ruitenbeek et al. (1995)
3	Not reported	Not reported	12	15–53	Mayell et al. (2007)
6	38	35–84	13	24–63	Raymond et al. (1999)
9	36	30–65	10	Not reported.	Duran et al. (1986)
12	22.0	26–66	14.4	21.0–53.0	Bodman et al. (2001)

defects in the acyl-CoA dehydrogenase family and were found to have a less severely reduced palmitate oxidation, though this may not be a true representation owing to the short period of non-supplementation prior to the study (Bergmann et al. 2001). The authors propose from that study that long-chain acyl-carnitines are the accumulated metabolites in heart, which have been thought to be arrhythmogenic (Oliver 2006; Yamada et al. 1994). Animal models have shown that ventricular arrhythmias may be induced via injection of long-chain saturated fatty acids (Soloff 1970). The development of arrhythmias may also be a consequence of the instability of the membrane resulting from the accumulated acyl-CoA derivatives (Oliver 2006). In summary, the production of toxic intermediates in a patient with a deficiency in β-oxidation may predispose the patient to cardiac arrhythmias.

Cardiac arrhythmias are not normally a symptom associated with MCADD (Bergmann et al. 2001; Bonnet et al. 1999). In a cohort of 107 patients diagnosed with a fatty acid oxidation defect over a 25-year period, 24 presented with arrhythmias as their first symptom. Bonnet and colleagues (1999) observed no patient with MCADD, primary carnitine deficiency (organic cation transporter-2 deficiency) or carnitine parmitoyltransferase I (CPT I) deficiency having arrhythmias. However, cardiac arrhythmias have been reported in a number of CPT I deficiency cases, especially in the neonatal and infantile period (Bergmann et al. 1994; Olpin et al. 2001; Schaefer et al. 1997). One case of ventricular fibrillation has been reported in a 15-year-old girl of consanguineous Iranian parents with primary carnitine deficiency who presented without overt cardiomyopathy (Rijlaarsdam et al. 2004). Ventricular arrhythmias continued until her carnitine levels normalized. Similarly to MCADD, there is no accumulation of long-chain fatty acyl-carnitines in the mitochondria in this condition either. Rijlaarsdam and colleagues (2004) hypothesize that deficiency of carnitine in later life may itself cause electromyocardial changes. In case 1 and case 5, the patients' cardiac symptoms resolved following carnitine supplementation and were absent on follow-up. In both the study of Lafolla and colleagues (1994) and this case series, the prevalence of cardiac arrhythmias was approximately one-third and suggests that they further research is appropriate to determine why they are increased in MCADD.

Rhabdomyolysis

Muscle weakness and rhabdomyolysis are not normally observed in MCADD but are commonly seen in VLCAD, LCHAD, MTP, and CPT II deficiency. However Lafolla and colleagues (1994) reported 9 patients (7.5%) who presented with muscle weakness and associated raised creatine kinase levels and who were older at diagnosis (>3 years of age). Derks and colleagues (2006) also reported on follow-up that 35% of patients reported fatigue, 31% muscle pain and 39% reduced exercise intolerance. One-third of acute adult cases in this series presented with rhabdomyolysis, which may be associated with the cause of the metabolic stress, e.g. strenuous exercise or alcohol ingestion. All these patients experiencing chronic complaint were homozygous for the common gene mutation (985A>G) similarly to the cases discussed in this review (Derks et al. 2006).

Steatosis

Five of the acutely presenting adults had evidence of fat deposition in a number of tissues, particularly the liver, heart muscle and kidney, similar to that of infantile cases (Lafolla et al. 1994). Presence of such pathology in an infantile postmortem examination would prompt the investigator to exclude a possible fatty acid oxidation disorder. However, the aetiology of adult fatty liver is varied and includes non-alcoholic causes related to lifestyle (Saito et al. 2007). It is therefore important for the pathologist to note non-alcohol-related causes of steatosis, especially in an acute, unexpected death.

There has been a long-recognized association with AFLP and the syndrome of haemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) with LCHAD (Ibdah et al. 2000). There has also been risk identified in those mothers carrying a fetus having a short-chain or medium-chain defect (Browning et al. 2006). In this case series two patients were pregnant at the time of investigation, one being investigated for AFLP (Santos et al. 2007). It is therefore important that maternal disease is excluded as a possible cause in addition to a fetal disease in such pregnancies, and careful management of future pregnancies is important. However, one patient once diagnosed had three successful pregnancies without any additional support (T. Derks, personal communication, 2009).

Summary

In the absence of population screening, adults with undiagnosed MCADD can be expected. They are at risk of sudden fatal metabolic decompensation with high mortality. The mortality of infantile cases is approximately 25% (Derks et al. 2006; Touma and

Charpentier 1992; Wilcken et al. 1994) whereas this adult case series has shown it to be 50% in acute cases and 29% in total. This review illustrates the need to consider the possibility of a fatty acid oxidation defect in an adult who presents with unexplained sudden clinical deterioration, particularly if precipitated by fasting or alcohol consumption. A history of unexplained sibling death may also raise the index of suspicion. There also needs to be appropriate clinical support for those patients identified clinically or as a result of family studies (sibling or parent). Long-term outcome studies of MCADD are limited and it is possible to speculate that in later life some undiagnosed cases may present with symptoms similar to those of chronic alcoholism, e.g. cirrhosis and steatosis. It is also important to note that that the long-term outcome of those cases identified through neonatal screening or during infancy is dependent on appropriate clinical management and support (Leonard and Dezateux 2009).

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