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MEDIUM CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (MCADD) FOLLOW-UP IN ADULTS

MCADD is a rare inherited metabolic disorder of mitochondrial β-oxidation of fatty acids. It is the most common fatty acid oxidation disorder with the highest incidence in Northern Europe and with a prevalence of around one in 10,000-27,000.[1]

It is due to a deficiency of the enzyme medium chain acyl CoA dehydrogenase which is needed for the oxidation of medium chain fatty acids (carbon chain length C6-C12).[1,2]

There is no chronic manifestation, but in times of catabolic stress (illness, infection, fever, fasting, poor calorie intake), the body is unable to utilise medium chain fatty acids for energy effectively, leading to a build-up of toxic metabolites which can lead to drowsiness, encephalopathy, seizures, brain, muscle and liver damage, as well as coma and even death.

NEW BORN SCREENING

MCADD is now one of the inherited disorders that is screened for during new born screening (NBS) in the first week of life. Screening in England has been in place since 2009, followed by the rest of UK by 2012.[1] Prior to screening, infants were commonly diagnosed when they presented with hypoketotic hypoglycaemia (from an accumulation of free fatty acids and impaired gluconeogenesis) and mortality was high.[3] Metabolic decompensation was triggered by acute illness such as fever, vomiting, diarrhoea and prolonged fasting. Age at presentation ranged from a few days of life to adulthood. NBS significantly reduced clinical manifestation and death in MCADD in the Australian NBS program. Risk of death or a severe event by two years was 5% in the screened cohort vs 55% in the unscreened cohort.[4]

MANIFESTATION IN ADOLESCENCE AND ADULTS

As screening for MCADD is only recent, there is a possibility of older children and adults having the MCADD gene and being unaware. Undiagnosed people are asymptomatic until an episode of increased energy demand and fasting occurs, resulting in a metabolic crisis.[2] Manifestation in adolescence and adults has been reported (16 to 45 years), see Table 1 overleaf.

All of the presentations were acute with multiple organ involvement and signs of decompensation which occurred due to metabolic stress. Out of the eight presentations described, half presented due to alcohol ingestion which resulted in vomiting. The rest were due to strenuous exercise without adequate nutrition, illness, surgery and pregnancy. Hypoglycaemia was only found in 50% of adult presentations,[3] so normoglycaemia should not be relied on as an indicator of metabolic stability.

TREATMENT: INFANTS - NEW BORN SCREENING (NBS)

Once infants have been diagnosed via NBS, then they should be seen in hospital by the specialist medical team 24 to 48 hours after the positive screening result. Advice should be given by the dietitian on safe fasting times (Table 2) and an emergency regimen given for times of illness and decreased milk/food intake.[5]

The emergency regimen (ER) is a glucose polymer drink given at least every three hours day and night to

Table 1: Severe first presentation of MCADD in adults[3]

Gender	Age of presentation	Presented with	Cause of metabolic stress
Male	30 years	Acute encephalopathy and rhabdomyolysis.	Strenuous exercise in the cold without adequate nutrition.
Female	19 years	Lethargy, disorientation and vomiting, died from cardiopulmonary arrest 24hrs later.	Vomiting following ingestion of alcohol and marijuana.
Female	16 years	Acute encephalopathy, deteriorating rapidly to coma.	Alcohol binge with starvation and vomiting.
Female	23 years	Severe vomiting, abdominal pain and encephalopathy. Died from cardiac arrest.	Heavy bout of drinking alcohol.
Male	33 years	Lethargy, vomiting and headaches. Led to encephalopathy and cardiac arrest, which he survived.	Chronic alcoholism.
Female	45 years	Nausea, mild hypoglycaemia leading to encephalopathy and death from respiratory arrest.	Third day post operatively following successful colon resection to remove adenocarcinoma. Five pounds weight loss prior to surgery.
Female	16 years	Found unresponsive at home, hypoglycaemic and raised ammonia, died shortly after.	One day history of nausea and vomiting following upper respiratory tract infection.
Female	29 years	Suspected acute fatty liver of pregnancy.	39 weeks gestation.

prevent the body using medium chain fatty acids as an energy source. The amounts and percentage of carbohydrate given depends on age (Table 3). If the ER is refused, then the child should have rapid access to their local paediatric services and avoid waiting in emergency rooms, so that there is no delay in starting an intravenous drip containing 10% glucose.

TREATMENT: ADULTS

Diet in MCADD is a normal healthy diet (no need to restrict fat), regular meals with starchy carbohydrate, avoidance of medium chain triglyceride (MCT) containing products (including sip feeds and nutritional feeds containing MCT) and avoidance of prolonged fasts. Small amounts of coconut as ingredients may be tolerated, but to avoid pure coconut and coconut oil.[1]

Normal diets contain predominantly long chain fats (carbon chain length C16-18).These long chain fatty acids undergo β-oxidation to release energy and their carbon length decreases to a medium and then short chain fatty acid length.

Under normal conditions, the oxidation of medium chain fatty acids have been reported to be near normal in patients with MCADD due to over lapping substrate enzymes. This only becomes a problem when there is an increased demand for fatty acids to provide energy such as illness or fasting.[1]

ILLNESS

There is a high risk of decompensation during illness due to increased energy expenditure and decreased food intake/increased fasting times. During illness,

Table 2: Safe fasting times[5]

Age	Hours
<4 months	6 hours
4-8 months	8 hours
8-12 months	10 hours
12 months+	12 hours

Table 3: Carbohydrate % of emergency drinks[5]

Age	% of carbohydrate in emergency drinks
<1 year	10%
1-2 years	15%
>2 years	20%
>10 years	25%

Table 4: Carbohydrate polymers that can be used to make a 25% carbohydrate solution for Emergency regimen for >10 years[8]

Carbohydrate Polymer
S.O.S.25 (Vitaflo)
Vitajoul (Vitaflo)
Maxijul Super Soluble (Nutricia)
Polycal powder (Nutricia)
Caloreen (Nestle)

high carbohydrate drinks must be consumed to prevent the body using medium chain fatty acids as an energy source. In adults, 200mls of a 25% carbohydrate drink should be taken every two to three hours during the day. If the illness is severe, they must continue to take the drinks throughout the night.[7] The emergency drink is preferably made from a carbohydrate polymer (Table 4).

In our centre, we now routinely recommend the use of pre-measured sachets of glucose polymer to make up the emergency feed as they are a more accurate method, especially in times of stress.[6] A supply of the glucose polymer should be available on prescription and kept at home. If glucose polymer is unavailable, then commercial high sugar drinks can be used, but more will have to be consumed as the percentage carbohydrate content is lower (Table 5 overleaf). Care must be taken not to use sugar-free or diet drinks as the carbohydrate content will be minimal. We advise patients to call their metabolic centre for advice if they are worried or are using their emergency regimen for over 24 hours without getting better. If they cannot tolerate their emergency drinks (due to frequent vomiting or diarrhoea) then they must go immediately to hospital (via emergency department) for intravenous glucose. When presenting themselves to their local emergency department, they should bring an emergency letter from their medical team (to ensure that they are seen quickly and started on intravenous 10% glucose), a copy of their nutritional emergency regimen and supply of their emergency drinks. Patients should not continue longer than 48 hours on a carbohydrate emergency regimen as they can become nutritionally deficient.[7]

ALCOHOL AND DRUGS

During adolescence, a big risk factor is alcohol and drug consumption, especially binge drinking and vomiting. Alcohol consumption may lead to vomiting, hypothermia and hypoglycaemia (by inhibiting gluconeogenesis) which is dangerous, as energy generation from fatty acid oxidation is impaired in times of stress.[2] Education should be given on healthy drinking guidelines: avoiding binge drinking, eating before, during and after alcohol/nights out (especially if clubbing), telling a friend about their MCADD so it is not mistaken for being drunk and to carry a wallet ID card for identification and treatment.

WEIGHT MANAGEMENT

Patients should be advised to avoid crash dieting and losing weight quickly. Weight loss should be slow and steady, avoiding any long

Table 5: Carbohydrate content of commercial drinks

High sugar drink	% Carbohydrate
Lucozade	17%
Coke	10%
Orange juice	10%
Ribena	10%

periods of fasting and under the care of the specialist dietitian.

COMPETITIVE SPORT

Patients with MCADD can tolerate moderate intensity activity without impairing fatty acid oxidation.[9] It should be advised that if the patient undertakes competitive or strenuous sport they should ensure that they have regular and sufficient food intake and food composition should be adjusted to the patient's needs.[2]

SURGERY

If any surgery or medical procedure requires a period of fasting, then the patient must contact their metabolic team who can provide a management plan to their surgical/medical team. Often, the patient will need to be on an intravenous 10% glucose drip during the period of fasting and the procedure. The intravenous glucose must not be stopped until the patient is eating and drinking well post procedure. During anaesthetics, consideration should be given to avoiding propofol and succinyl choline due to their potential risk of precipitating myopathy.

PREGNANCY

Morning sickness can be a problem in MCADD. Dietary advice should be given to help manage morning sickness and a low threshold for the use of anti-sickness medication. If morning sickness is severe, then the patient may need to be admitted to hospital for intravenous glucose. Planning for labour is important; patients should ensure that they have plenty of snacks and glucose polymer in their hospital bag. A medical plan is needed in case of prolonged/difficult labour or planned/emergency caesarean section.

FUTURE CHALLENGES

Patients who were diagnosed after a de-compensation will be well aware of the risks of MCADD. There is concern that the newly screened population may enter adolescence, viewing themselves as healthy and forget about the risks of illness or alcohol consumption. Annual clinic visits are important to continue to educate them and update their emergency plan. Patients should be encouraged to keep wallet medical ID cards (with diagnosis, first line treatment and hospital contact), or a medical bracelet, to aid management and treatment in times of decompensation when they are with people who are unaware of their condition. Ensure that they have up-to-date emergency contact numbers and letters to take to hospital if unwell, to prevent long waiting periods in the emergency room.

CONCLUSION

There is a growing number of screened children with MCADD who will move through into adolescence and adulthood. It is important not to medicalise these patients, but we also do not want them to forget the risk of decompensation. If they look after themselves, attend regular clinics and manage illness, then they can live a normal life.

There is also the possibility that there are adolescents and adults who are undiagnosed with MCADD and they are at risk of sudden metabolic decompensation and high mortality. Fatty acid oxidation defect needs to be considered as a possibility in adults who present with unexplained sudden deterioration, particularly if precipitated by fasting or alcohol consumption.

Useful resource

British Inherited Metabolic Diseases Group website: www.bimdg.org.uk for emergency management (medical and dietetic) and MCADD guidelines for dietitians.