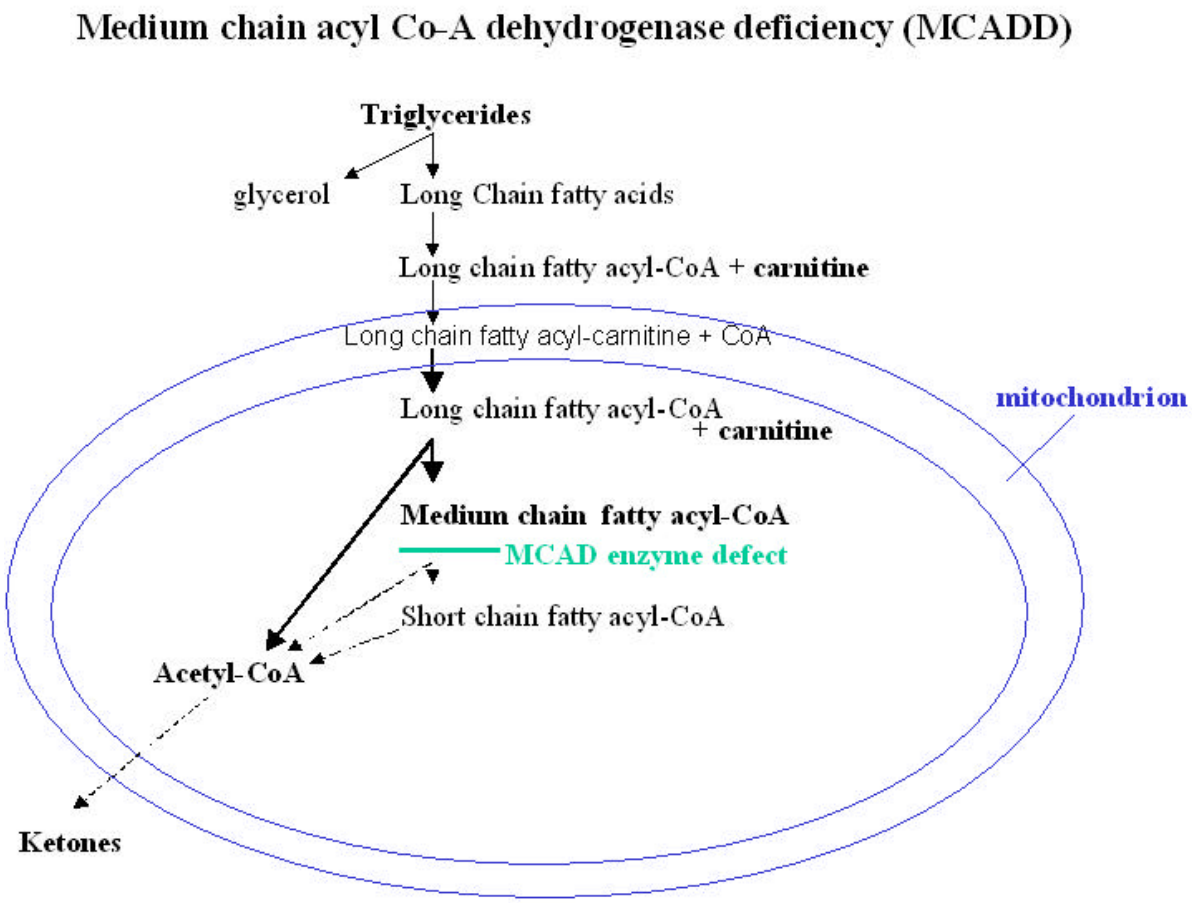
ACUTE ILLNESS PROTOCOL
FATTY ACID OXIDATION DISORDERS
MEDIUM CHAIN Acyl-CoA DEHYDROGENASE (MCAD) DEFICIENCY

INTRODUCTION

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) is the most frequent of the fatty acid oxidation disorders (FAOD) and one of the most frequently identified inborn errors of metabolism. The incidence of MCADD may be as high as 1/10,000 with mortality rates of 13-43% at initial crises. It is caused by an intramitochondrial defect in the β-oxidation of fatty acids and is a major cause of hypoketotic hypoglycemia. MCADD is also a cause for lethargy, liver dysfunction with hepatomegaly, metabolic acidosis, hyperammonemia and sudden death.

PATHOPHYSIOLOGY

Below is the fatty acid β-oxidation metabolic pathway indicating the MCADD block.



The pathophysiological process begins with reduced glucose intake as a result of a fasting state or increased energy needs from a catabolic state (infection, stress, fever, etc…) not sufficiently provided for by caloric intake. The resulting hypoglycemia leads to mobilization of free fatty acids (FFAs) from adipose tissue which enters the mitochondria via the carnitine cycle. In the mitochondria, as shown in the diagram above, the fatty acids in the acyl-CoA form are normally oxidized to acetyl-CoA which is used to produce the ketones that can supply the energy needs to compensate for the lack of adequate glucose. The block at MCAD prevents oxidation of medium chain CoA to short chain CoA, thereby markedly reducing the production of ketones. This block also results in the accumulation of fatty acid intermediates that inhibit gluconeogenesis (thus preventing endogenous glucose production), have a toxic effect on the liver and produce metabolic acidosis.

CLINICAL PRESENTATION

- Lethargy
- nausea or vomiting
- hypoglycemia with lack or only 'trace' of urinary ketones
- hepatomegaly
- 'Reye' like syndrome
- seizures
- coma
- near/rescued SIDS

Affected infants and children usually present between 3 and 24 months of age particularly when being weaned from nighttime feeds but neonatal cases have been described and adults have become ill after severe exertion (e.g. jogging). The presentation is characterized by **marked lethargy,** often in association with vomiting after a period of fasting. This can progress to hypoglycemic seizures or coma within 1-2 hours of ONSET of symptoms. On occasion seizures or coma may be the presenting sign. Hepatomegaly is usually present. There may, or may not, be a history of a recent viral infection associated with diminished oral intake, or of a similar episode in the past. A history of "recurrent Reye syndrome" should alert you to the possibility of FAODs, as affected children have often been misdiagnosed as having Reye syndrome or 'episodic hypoglycemic coma'; FAODs are responsible for 5-10% of sudden infant death syndrome. Immediate attention and therapy is the key to preventing sudden death.

NOTE that in the acute crises patients can be seriously ill WITHOUT hypoglycemia although typically FAOD crises are associated with hypoglycemia. At these times the urine typically tests 'absent' or 'small' for the presence of ketones. Liver function tests may be mildly elevated; hyperammonemia and hyperuricemia are often present during acute episodes.

Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children. Listen to them !!!

ASSESSMENT

Assess for dehydration, fever, infection or any other physical stressor e.g. surgery, as a potential precipitant for metabolic decompensation. As a rule, decompensation occurs more quickly in infants but children and adults, though more resistant, are still at risk of sudden death.

- **Blood glucose**
- **Electrolytes, CO_2** and **blood gas**
- **Ammonia** (1.5 ml blood in sodium-heparin tube sent STAT to lab on ice)
- **LFTs** (AST,ALT,AlkPO_4 PT,PTT, bilirubin)

* * ALL siblings of known cases should be tested for MCADD whether or not they have a history of symptoms.

TREATMENT

1. INDICATION FOR IV (NEVER less than 10% dextrose IV infusion)
(One or more indication is sufficient for IV)

- Vomiting
- Hypoglycemia
- Poor PO intake
- Dehydration Do not rely on urinary ketones as indicating dehydration!
- Decreased alertness
- Metabolic Acidosis

Start 10% glucose continuous infusion at 1.5x maintenance, to provide 7-8mg/kg/min.

2. HYPOGLYCEMIA

push 25% dextrose 2ml/kg and follow with a continuous 10% dextrose infusion at 1.5x maintenance, to provide 7-8 mg/kg/min glucose.

3. METABOLIC ACIDOSIS (Bicarbonate level <16mEq/L)

must be treated aggressively with IV sodium bicarbonate (1mEq/kg). Treating conservatively in the expectation of a re-equilibration of acid/base balance as other biochemical /clinical parameters are normalized can lead to tragic consequences.

4. PRECIPITATING FACTORS

Should be treated aggressively to help minimize further catabolism

5. APPARENTLY WELL

If drinking oral fluids well, and none of the above factors present, there is no need for emergent IVI. But history of earlier vomiting, pyrexia, or other stressor should be taken seriously and a period of observation undertaken to ensure that PO fluids are taken frequently and well tolerated, with glucose status monitored periodically.

POST EMERGENCY MANAGEMENT

1. Child unable to take/maintain PO intake
   - Start, or continue, 10% glucose continuous infusion at 1.5x maintenance.
   - Blood glucose and acid/base status should be monitored regularly. If the child is physically stressed keep the blood sugar levels elevated (glucose levels should be kept between 120-170 mg/dl)

2. Carnitine

The use of carnitine in FAODs is controversial and there are concerns that excessive long chain acyl carnitines which may be produced may induce arrhythmias. Consult with the metabolic physician for guidance regarding this in each individual case.

3. **DO NOT ADMINISTER LIPIDS IN ANY FORM**

4. Other medications

Epinephrine may stimulate lipolysis, therefore if indicated in these children should be covered with 10% dextrose infusion. It is wise to check drug interaction and side effects such as hypoglycemia whenever prescribing for these children.

5. Avoidance of fasting when stop IVI

   this may include complex carbohydrate in the form of cornstarch supplementation to get through the night as the child gets older and a high carbohydrate/low fat diet.

Any questions about the patient or this protocol, please call or have paged the Genetics/Metabolism Fellow-on-call or, failing this, the Metabolic attending on call at your hospital or nearest pediatric tertiary care center.

Additional information may be obtained via OMIM at
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=201450