

ACUTE ILLNESS PROTOCOL
FATTY ACID OXIDATION DISORDERS
VERY LONG CHAIN ACYL CoA DEHYDROGENASE (VLCADD) DEFICIENCY

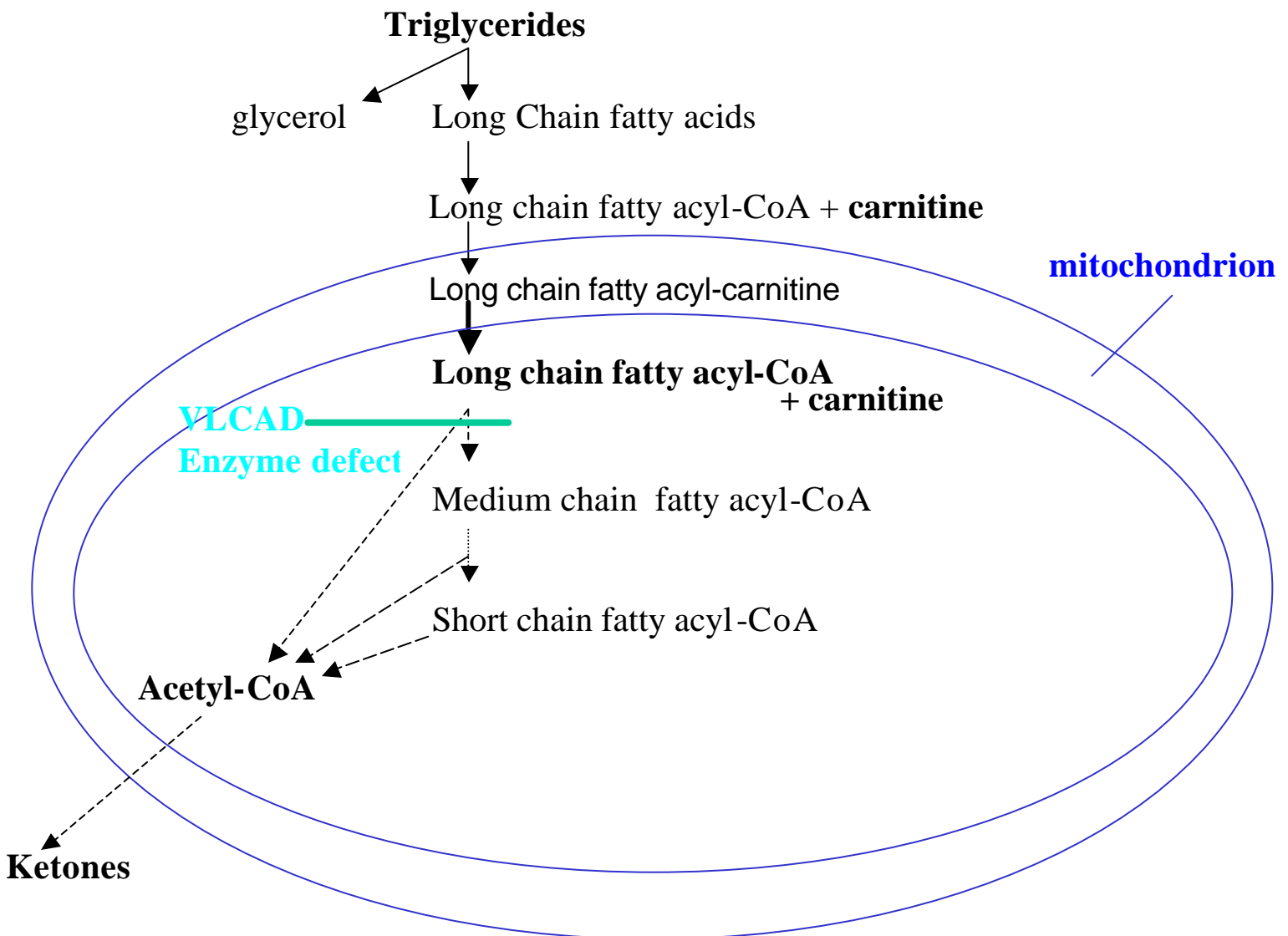
INTRODUCTION

Very long Chain Acyl CoA Dehydrogenase Deficiency (VLCADD) is an autosomal recessive disorder resulting in an intramitochondrial defect in the β -oxidation of fatty acids. It can cause severe hypoketotic hypoglycemia, encephalopathy, lethargy, liver dysfunction with hepatomegaly, cardiomyopathy metabolic acidosis, hyperammonemia and sudden death.

PATHOPHYSIOLOGY

Below is the fatty acid β -oxidation pathway indicating the VLCADD block

Very Long chain acyl Co-A dehydrogenase deficiency (VLCADD)



PATHOPHYSIOLOGY

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, etc...) not sufficiently provided for by caloric intake. The resulting hypoglycemia leads to mobilization of free fatty acids (FFAs), which enter the mitochondria via the carnitine cycle. In the mitochondria, as shown in the diagram above, the fatty acids in the acyl Co-A 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. A deficiency of VLCAD however prevents ketone formation. The block at VLCAD 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. Muscle, particularly myocardium, requires a lot of energy and, therefore, becomes functionally impaired resulting in lethargy, hypotonia and hypertrophic cardiomyopathy.

CLINICAL PRESENTATION

- Nausea or vomiting
- Lethargy
- Hypoglycemia with lack or only 'trace' of urinary ketones
- Seizures
- Hepatomegaly
- 'Reye' like syndrome
- cardiomyopathy, arrhythmias
- coma
- near/rescued SIDS

First presentation can occur in the neonatal period but more often when the infant is being weaned from night time feeds. The usual picture is nausea, vomiting and/or lethargy after a period of fasting. This can progress to hypoglycemic seizures or coma within 1-2 hours of ONSET of symptoms. 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. FAODs are responsible for a small but significant proportion of sudden infant death syndrome, which may be preventable with prompt early recognition and treatment.

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/ INVESTIGATIONS

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** (?hypoglycemia)
- **Electrolytes, CO₂ and Blood Gas** (?metabolic acidosis)
- **Ammonia** (1.5 ml blood in sodium-heparin tube sent STAT to lab on ice)
- **LFTs** (AST, ALT, AlkPO₄, PT, PTT, bilirubin)

TREATMENT

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

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

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

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. Cardiology

A cardiology assessment is necessary to properly evaluate a child with acute symptomatic VLCADD, specifically for heart failure or pericardial effusion. Should cardiology not be available the **minimum** evaluation required would be a CXR and EKG

3. Carnitine

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

4. Medium Chain Triglyceride (MCT) Oil

MCT oil provides a high calorie substrate for the patient with **confirmed** VLCADD by bypassing the block in β -oxidation. **HOWEVER**, the diagnosis of VLCADD must be certain as MCT oil **will exacerbate**, and may be highly dangerous, to patients with other fatty acid oxidation defects.

5. 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.

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=201475>