Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD)

The acute illness materials are a guideline for healthcare professionals treating the sick infant/child who has previously been diagnosed with very long chain acyl-CoA dehydrogenase deficiency (VLCADD), a long chain fatty acid oxidation disorder (LC-FAOD). These materials were originally developed at Boston Children's Hospital under the direction of Dr. Harvey Levy, Senior Physician in Medicine/Genetics and Dr. Jonathan Picker, Fragile X Program Director and were most recently updated in 2020 by Dr. Amy Kritzer.

Disclaimer: Metabolic crises in infants and children with FAOD are complex medical emergencies and must be treated as such to avoid death or serious brain injury. This protocol is only a guideline and should NOT be used for definitive treatment without metabolic consultation. It is essential to call or page the on-call genetics/metabolism fellow, or failing this, the on-call metabolic attending at your hospital or nearest pediatric tertiary care center, as rapidly as possible. Please read our Terms of Use.

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, arrythmia, rhabdomyolysis and sudden death.

PATHOPHYSIOLOGY

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

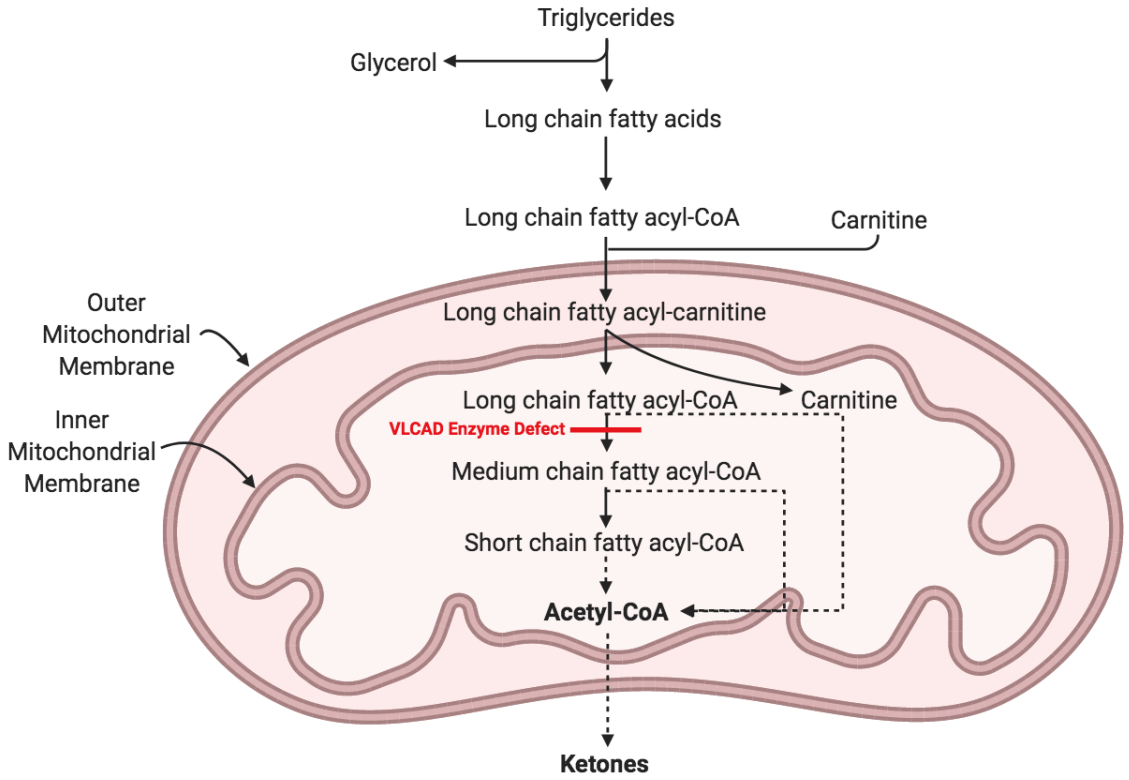

Figure created with BioRender.com

The pathophysiological process begins with reduced glucose intake as a result of a fasting state or increased energy needs from a catabolic state (e.g., infection, fever, stress, etc.). 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 and 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, rhabdomyolysis, and hypertrophic cardiomyopathy.

CLINICAL PRESENTATION:

- Nausea or vomiting
- Lethargy
- Hypoglycemia with absence of or only 'trace' urinary ketones
- Seizures
- Hepatomegaly
- 'Reye' like syndrome
- Cardiomyopathy, arrhythmias
- Coma
- Near/rescued SIDS

NOTE: In an acute crisis, patients can be seriously ill WITHOUT hypoglycemia. Elevated liver enzymes and/or creatine kinase levels may the most prominent laboratory abnormality(ies).

The first presentation can occur in the neonatal period but occurs more often when the infant is being weaned from night time feeds. The usual presentation includes 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 proportion of sudden infant death syndrome, which may be preventable with prompt early recognition and treatment.

Parents of children with diagnosed metabolic disorders know the signs of decompensation in THEIR children. It is important to listen to the parents' insight into their child's illness.

INITIAL 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 resilient, are still at risk of sudden death.

Laboratory:

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

EMERGENCY MANAGEMENT

Contact the on-call metabolism team at your hospital or nearest pediatric tertiary care center early in the course of evaluation.

1. Indication for Intravenous (IV) Dextrose

One or more indication is sufficient to start IV dextrose:

- Vomiting
- Poor oral intake
- Dehydration - Do NOT rely on urinary ketones as an indicator for dehydration!
- Decreased alertness
- Hypoglycemia*
- Metabolic Acidosis

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

If blood glucose rises > 170 mg/dL (or above your institution's acceptable range) with IV dextrose infusion, begin insulin infusion at 0.05-0.1 unit/kg/hour until blood glucose is controlled.

***NOTE**: IV dextrose is often necessary even if blood glucose is normal. Acute decompensation is not always accompanied by hypoglycemia.

2. Hypoglycemia

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

3. Metabolic Acidosis (Bicarbonate level <16mEq/L)

Metabolic acidosis 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

Precipitating factors should be treated aggressively to help minimize further catabolism.

5. Apparently Well

Many patients may appear clinically well even in the setting of an acute decompensation. It is important to ensure adequate calorie intake either through IV dextrose and/or oral intake as tolerated. 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. Creatine kinase levels should be followed during the observation period.

POST EMERGENCY MANAGEMENT

1. Child unable to take/maintain PO intake

- Start, or continue, a minimum of 10% glucose continuous infusion at 1.5x maintenance.
- Blood glucose, CK and acid/base status should be monitored regularly. If the child has ongoing stressors, such as fever, aim to keep blood sugar levels 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 chest X-ray and electrocardiogram.

Heart failure can be very acute. Any signs of tachycardia, shortness of breath or poor perfusion should be evaluated. **Have a low threshold to obtain an echocardiogram and/or BNP level**.

NOTE: VLCADD-related heart failure is often reversible with aggressive caloric supplementation and supportive therapy.

3. Medium Chain Triglycerides (MCT)

A source of MCT provides a high calorie substrate for the patient with confirmed VLCADD by bypassing the block in ß-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(e.g., medium chain acyl-CoA dehydrogenase deficiency).

There are many MCT products* currently available including MCT oils, powders, emulsified oils and triheptanoin.

*Examples of MCT products available in the United States (TABLE #6: Sources of Medium Chain Triglycerides)

4. Do not administer any long chain fat, such as IV intralipid, and avoid medications containing lipids, such as propofol. A source of essential fatty acids should be provided if long chain fat avoidance lasts for ≥7 days.

5. Carnitine

The use of carnitine in LCFAODs is controversial due to concerns that excessive accumulation of long chain acylcarnitines, which might be produced with carnitine supplementation, may induce arrhythmias. Consult with the metabolic physician for guidance regarding carnitine supplementation in each individual case.

6. Other medications

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

7. Weaning IV Fluids

It is important to wean off of IV fluids in a step-wise manner to avoid rebound hypoglycemia.

REFERENCES/ RESOURCES:

Additional information on the Southeast Newborn Screening and Genetics Network (SERN) and Genetic and Metabolic Dietitians International (GMDI) VLCADD Management Guidelines and Toolkit may be obtained here (https://southeastgenetics.org/ngp/).

Van Calcar SC, Sowa M, Rohr F, Beazer J, Setlock T, Weihe TU, Pendyal S, Wallace LS, Hansen JG, Stembridge A, Splett P, Singh RH. Nutrition management guideline for very-long chain acyl-CoA dehydrogenase deficiency (VLCAD): An evidence- and consensus-based approach. Mol Genet Metab. 2020 Oct 6:S1096-7192(20)30201-8.

Leslie ND, Valencia CA, Strauss AW, Zhang K. Very Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; May 28, 2009.