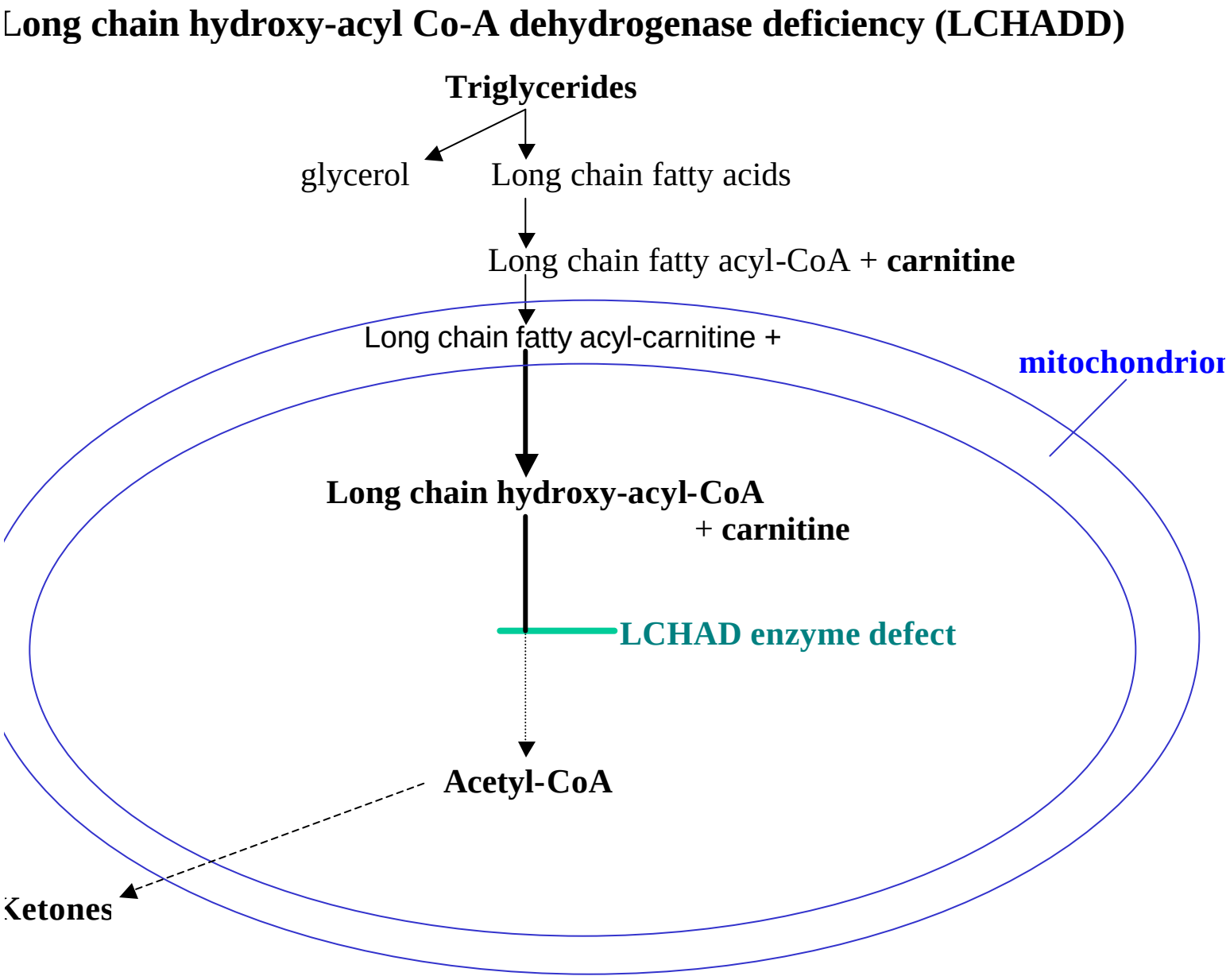
ACUTE ILLNESS PROTOCOL
FATTY ACID OXIDATION DISORDERS
LONG CHAIN HYDROXY Acyl-CoA DEHYDROGENASE DEFICIENCY (LCHADD)

INTRODUCTION

LCHADD is caused by a defect in the intramitochondrial β-oxidation of fatty acids. It can cause severe hypoketotic hypoglycemia, lethargy, liver dysfunction with hepatomegaly, clotting defect, metabolic acidosis, hyperammonemia cardiomyopathy, and sudden death.

PATHOPHYSIOLOGY

Below is the fatty acid β-oxidation metabolic pathway indicating the LCHADD 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 satisfied 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 hydroxy 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 LCHAD however, prevents this. The block at LCHAD 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 (including lactic) acidosis. Muscle, particularly myocardium, requires a lot of energy and, therefore, becomes functionally impaired resulting in lethargy, hypotonia and cardiomyopathy.

PRESENTATION

- Hypotonia and weakness
- Lethargy
- Hypoglycemia with absence or 'trace' ketones
- developmental delay
- peripheral neuropathy
- retinitis pigmentosa
- seizures
- hepatomegaly with liver dysfunction (rarely liver failure or cirrhosis)
- coagulopathy
- cardiomyopathy
- 'Reye' like syndrome
- coma
- sudden death

Affected infants and children usually present by 2 years of age. However, neonatal cases do occur. Conversely some patients will not present until adulthood with myoglobinuria and peripheral neuropathy. LCHAD is frequently precipitated by intercurrent illnesses. Children or their sibs affected with fatty acid oxidation disorders have often been misdiagnosed as having Reye syndrome or idiopathic cardiomyopathy; some who have died have also been labeled as SIDS deaths. Such family history should be viewed as suspicious for FAOD.

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.

ASSESSMENT

Assess for cardiorespiratory stability, dehydration, fever, infection or any other physical stressor (e.g. surgery), as a potential precipitant for metabolic decompensation. Assess hepatic and neurological status.

- **Blood glucose**
- **Electrolytes, CO_2** and **blood gas**
- **Ammonia** (1.5 ml blood in sodium-heparin tube sent STAT to lab on ice)
- **Lactate**
- **LFTs** (AST,ALT,AlkPO_4, bilirubin)
- **Clotting studies** (PT, PTTK)
- **EKG and CXR** for preliminary cardiac assessment. Cardiomyopathy is often present. If there is a past history of cardiomyopathy or current cardiac concerns, cardiology services should be notified immediately for emergency evaluation and input for management.

TREATMENT

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

- Vomiting
- Hypoglycemia
- lactic acidosis
- Poor PO intake
- Dehydration do not rely on urinary ketones as indicating dehydration!
- Decreased alertness
- Metabolic Acidosis
- Cardiac decompensation

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. CARDIAC CONSIDERATIONS

A cardiology assessment is necessary to properly evaluate a child with acute symptomatic LCHADD (specifically for heart failure or pericardial effusion).

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 acylcarnitines 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. 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.

LCHADD chronic management is complicated as many children take a significant amount of time (days to weeks) to improve clinically even once their biochemical parameters have normalized. Particular problems include improvement in mental status, hypotonia, hepatomegaly and cardiomyopathy. It is important to be aware that despite therapy children with LCHADD have died or been left with chronic neurologic, cardiac and hepatic problems. Though the long-term prognosis for children with LCHADD is unclear treatment can be optimized by:-

- avoidance of fasting (this may include complex carbohydrate in the form of cornstarch supplementation to get through the night as the child gets older)
- high carbohydrate/low fat intake
- Early detection of physiologic stresses inc. infection, surgery with especial attention to REGULAR feedings/source of glucose AROUND the clock.
- Regular review by cardiology and ophthalmologic services.

Note that the pregnant mother carrying a fetus with LCHADD is at risk for the HELLP syndrome (hemolysis, elevated liver enzymes and low platelets). She should be closely followed up for counseling and antenatal care for future pregnancies as there will be a 25% risk of each future pregnancy having an affected LCHADD fetus.

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/htbin-post/Omim/dispmim?600890#TEXT