VERY LONG CHAIN ACYL CoA DEHYDROGENASE (VLCAD) DEFICIENCY

RECOMMENDATIONS ON EMERGENCY MANAGEMENT OF METABOLIC DISEASES

Department of Medical Genetics
**INTRODUCTION**

Very long Chain Acyl CoA Dehydrogenase Deficiency (VLCAD), an autosomal recessive disease, is a common disorder of fat breakdown. It is caused by an intra-mitochondrial defect in the β-oxidation of fatty acids and is a major cause of severe **hypoketotic hypoglycemia**. It can also cause encephalopathy, lethargy, liver dysfunction with hepatomegaly, cardiomyopathy, metabolic acidosis, hyperammonemia and sudden death.

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

For most of the time patients are healthy and do not require a special diet. However metabolic stress such as fasting and/or febrile illness particularly gastro-enteritis and flu can lead to serious illness, with encephalopathy and even sudden death. This results from the accumulation of toxic fatty acids 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.
**Note** ALL siblings of known cases should be tested for VLCAD whether or not they have a history of symptoms.

**PRESENTATION**

First presentation can occur in the neonatal period or when the infant is being weaned from night time feeds.

The early signs of decompensation include:

- Marked Lethargy
- Poor appetite
- Nausea
- Vomiting: is common and should always be taken seriously
- However, some signs may be difficult to assess such as **irritability** or just ‘**not right**’. Always listen to parents carefully; their knowledge might exceed your expectations.

Later signs and symptoms of decompensation may include:

- Change/Altered level of consciousness
- Hypoglycemia with lack or only ‘trace’ of urinary ketones:
  
  **Hypoglycemia only occurs at a relatively late stage (or very late) so that blood glucose should not be relied on. Do not delay treatment just because the blood glucose is not low. The aim should always be to intervene whilst the blood glucose is normal.**

  Treatment aims to prevent mobilization of fat by providing ample glucose enterally or intravenously

- Metabolic acidosis
- Hyperammonemia
- Cardiomyopathy, arrhythmias
- ‘Reye’ like syndrome
- Seizures
- Near/rescued SIDS
- Hepatomegaly
- Coma within 1-2 hours of ONSET of symptoms

**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; hyperammononemia and hyperuricemia are often present during acute episodes.
**INITIAL MANAGEMENT IN HOSPITAL**

Almost all patients who present to hospital will require admission. **If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation.**

Management decisions should be based primarily on the *clinical* status.

The first decision about therapy is whether the child can be treated orally or will need intravenous therapy.

- If the child is relatively well, may be treated orally but assess very carefully
- If the child is obviously unwell, must be treated with intravenous fluids.
- **If there is any doubt at all, put up an intravenous line**
- If the child is shocked or clearly very ill, arrange for admission to Intensive Care Unit

**ASSESSMENT**

As a rule, decompensation occurs more quickly in infants but children and adults, though more resistant, are still at risk of sudden death.

**a. Clinical assessment:**
- Vital signs, cardiovascular stability
- STAT glucocheck (blood sugar) to check for hypoglycemia
- Neurologic status (including Glasgow coma score);
- Hydration status
- Presence of fever; signs of infection
- Hepatomegaly

**b. Labs:**

**Blood**
- Blood gas (arterial or venous)
- Blood glucose
- Ammonia
- Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca++, PO₄, Mg)
- Urea, creatinine
- Creatine Kinase (CK)
- Liver profile (including AST, ALT, AlkPO₄, PT, PTT, bilirubin)
- CBC differential

**Urine**
- Urine dipstick for ketones

**Culture**

If patient is febrile, cultures of blood, urine, and/or throat are needed depending on the patient clinical presentation.
**TREATMENT**

1. **INDICATION FOR IV (NEVER less than 10% dextrose IV infusion).**

One or more indication is sufficient for IV:

- Vomiting
- Hypoglycemia
- Poor oral 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.

- Give Glucose 200 mg/kg **at once** (2 ml/kg of 10% glucose or 1ml/kg of 20% glucose) over a few minutes.
- Give normal saline 10 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give 20 ml/kg normal saline instead of the 10 ml/kg. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
- Continue with glucose 10% at 5 ml/kg/h until next solution ready. – see below
- Quickly calculate the deficit and maintenance and prepare the intravenous fluids
  - Deficit: estimate from clinical signs if no recent weight available
  - Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children) 100ml/kg for 1st 10kg then 50 ml/kg for next 10kg then 20ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.
  - Give 0.45% saline/10% glucose
- Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.
- Recheck the electrolytes every 24 hours if still on intravenous fluids.
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. Hyperglycemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using the local diabetic protocol for treatment of DKA rather than reducing the glucose intake. **Strict supervision is essential.**

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

5. 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 primary metabolic physician for guidance regarding this in each individual case.

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

7. PRECIPITATING FACTORS
Should be treated aggressively to help minimize further catabolism.

8. 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.
**MONITORING THE PATIENT**

Reassess after 4-6 hours or earlier if there is any deterioration or no improvement. If child is unable to take/maintain PO intake, start, or continue, 10% glucose continuous infusion at 1.5 x maintenance.

Clinical assessment should include:

- ✓ Mental status (Glasgow Coma Score)
- ✓ Vital signs
- ✓ Fluid balance
- ✓ Symptoms of infection

**Biochemical parameters:**

- ✓ Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca+++, PO₄, Mg)
- ✓ Ammonia
- ✓ Urea, creatinine
- ✓ Blood glucose
- ✓ Blood gases

**RECOVERY**

- The patient should be kept NPO, while on IV infusion, until his/her mental status is more stable.
- If the patient is not significantly neurologically compromised, enteral feeds (NG/GT) with the patient special formula should be introduced **as early as possible**, as this allows a much higher energy intake and reduces the risk of malnutrition
- If drinking oral fluids well, and none of the above factors present, there is no need for emergent IV infusion. 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.
- Avoidance of fasting when stop IV infusion: 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 is to be followed.
ACKNOWLEDGMENT
These recommendations have been compiled by Nahya Awada, Advanced Clinical Specialist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the American College of Medical Genetics (ACMG), the British Inherited Metabolic Disease Group (BIMDG), and the New England Consortium on Metabolic Programs; and have been revised by Medical Genetics Consultants in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011.

REFERENCES

- ACT SHEET (2010), American College of Medical Genetics (ACMG), Medical Genetics Translating Genes Into Health, [on line], Accessed on 01 August 2011
- EMERGENCY guidelines (2009), British Inherited Metabolic Disease Group (BIMDG) [on line], Accessed on 01 August 2011.
- Emergency Treatment Protocol- New England Consortium on Metabolic Programs, [on line], Accessed on 01 August 2010
Dietary Emergency Protocol for
Very Long Chain Co A Acyl Dehydrogenase Deficiency (VLCAD)

- Name:
- Date of birth:
- Weight & date of weight measurement:

1. Discontinue regular diet/feeds
2. If your child is able to take fluids orally, start giving emergency solution every 2 hours during the day and every 3 hours during the night as follow:
   Add ................ Scoops Polycose/Prophree to ................. mls water

3. If your child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if your child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the solution as:
   - Small boluses: Give ........ mls of emergency solution every .......... hour
   - Or continuously if a feeding pump is available
5. If a Rehydration Solution is to be given as in case of gastroenteritis:
   Add........... Scoops Polycose/Prophree to.......... mls of Rehydration Solution

6. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen:
      - If the child is doing well, go back to normal diet.
      - If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
b. Between 24 – 48 hours from starting the emergency regimen:

- If your child appears well, reintroduce regular formula then diet.
- If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.

c. After 48 hours from starting the emergency regimen:
If no improvement is noticed or if the child is not taking above prescribed amounts of emergency solution, bring your child to the hospital with all medicines, special dietary products, and scoops.

7. Try to offer MCT oil during crisis to your child.

N.B:

If, at any time from starting this emergency regimen, your child is deteriorating and/or not tolerating the emergency solution due to nausea and vomiting, bring your child immediately to the hospital with all medicines, special dietary products, and scoops.

**ACKNOWLEDGMENT**

Dietary Emergency Protocols have been compiled by Eman Megdad, Metabolic Nutritionist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the British Inherited Metabolic Disease Group (BIMDG), and have been revised by Medical Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011