TEXAS Department of State Health Services

Newborn Screening ACT Sheet

Elevated C4 and C5 +/- Other Acylcarnitines

Glutaric Aciduria Type 2 (GA2)

Differential Diagnosis: Glutaric aciduria type 2 (GA2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD); Ethylmalonic encephalopathy (EE), Riboflavin transporter defect.

Condition Description: GA2/MADD primarily affects fatty acid oxidation (FAO). FAO occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) when energy production relies increasingly on fat metabolism. GA2/MADD results from ETF/ETF-QO enzyme defects and subsequent inhibition of the proper function of FAO enzymes. EE is a related disorder that seems to be due to a defective mitochondrial matrix protein, the precise function of which is yet unknown. In these conditions, potentially toxic derivatives accumulate.

Conditions associated with this analyte have been identified by the Society of Inherited Metabolic Disorders (SIMD) as critical, and require immediate action.

MEDICAL EMERGENCY - You Should Take the Following IMMEDIATE Actions:

- **Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, odor of sweaty feet).**
- **Immediate telephone consultation with pediatric metabolic specialist (See attached list).**
- **Evaluate infant ("sweaty feet" odor, facial dysmorphism, failure to thrive, lethargy, hypoketotic hypoglycemia, metabolic acidosis, hyperammonemia). If signs are present or if infant is ill, initiate emergency treatment in consultation with a metabolic specialist.**
- **Initiate timely confirmatory/diagnostic testing as recommended by specialist.**
- **Initial testing: Plasma acylcarnitine profile, urine organic acids, and urine acylglycine analysis.**
- **Repeat newborn screen if the second screen has not been done.**
- **Educate family about signs and symptoms of hypoglycemia and metabolic acidosis ("sweaty feet" odor, facial dysmorphism, failure to thrive, lethargy, hypoketotic hypoglycemia, metabolic acidosis hyperammonemia).**
- **Report findings to newborn screening program.**

Diagnostic Evaluation: A specific diagnosis is established by plasma acylcarnitine, urine organic acid and acylglycine analysis. Plasma acylcarnitines will show multiple increased acylcarnitines with chain lengths of C4 C5 and higher. Urine organic acids will show a GA2 profile. GA2 can be confirmed with ETF/ETF-QO enzyme assay and gene sequencing. In Ethylmalonic encephalopathy (EE), elevated plasma acylcarnitines will only be C4 and/or C5 and urine organic acids will show increased ethylmalonic acid and isovalerylglycine. The diagnosis is confirmed by ETHE1 gene sequencing.

Clinical Considerations: GA2/MADD often presents in the neonate with poor feeding, marked lethargy, and facial and renal dysmorphism. Laboratory tests will reveal hypoketotic hypoglycemia, metabolic acidosis and hyperammonemia. Milder forms may present in childhood or later. EMA encephalopathy presents in infancy with developmental delay, diarrhea and petechiae.

Additional Information:

American College of Medical Genetics and Genomics
https://www.acmg.net/StaticContent/ACT/C4_C5.pdf

Genetics Home Reference
http://ghr.nlm.nih.gov/condition=glutaricacidemiatypeii

STAR G FELSI
http://www.newbornscreening.info/Parents/fattyaciddisorders/GA2.html
http://www.newbornscreening.info/Pro/fattyaciddisorders/GA2.html