Newborn Screening ACT Sheet
[Elevated 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).

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.

YOU SHOULD TAKE THE FOLLOWING ACTIONS IMMEDIATELY:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, odor of sweaty feet).
- Consultation/referral with pediatric metabolic specialist.
- Evaluate infant ("sweaty feet" odor, facial dysmorphism, failure to thrive, lethargy, hypoketotic hypoglycemia, metabolic acidosis, hyperammonemia). If signs are present of infant is ill, initiate emergency treatment in consultation with a metabolic specialist.
- Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- 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 finding 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:
Genetics Home Reference

Referral (local, state, regional and national):
Testing
Clinical Services
Find Genetic Services

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

LOCAL RESOURCES: Insert State newborn screening program web site links

State Resource site *(insert state newborn screening program website information)*

Name	
URL	
Comments	

Local Resource Site *(insert local and regional newborn screening website information)*

Name	
URL	
Comments	

APPENDIX: Resources with Full URL Addresses

Additional Information:

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

Referral (local, state, regional and national):

Testing
http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/16897?db=genetests&country=United%20States

Clinical Services
http://www.ncbi.nlm.nih.gov/sites/genetests/clinic?db=genetests

Find Genetic Services
http://www.acmg.net/GIS/Disclaimer.aspx

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