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

ACT Sheet

Newborn Screening ACT Sheet

[Elevated C4 and C5 +/- Other Acylcarnitines]

Glutaric Acidemia II (GA-II); also known as Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)

Differential Diagnosis: Riboflavin Metabolism Disorder (RMD); ethylmalonic encephalopathy (EE), nutritional riboflavin deficiency.

Condition Description: In GA-II and RMDs, electron transfer from dehydrogenases to the respiratory chain is disrupted causing secondary impairment of multiple enzymes involved in mitochondrial fatty acid oxidation (FAO) and other energy producing pathways. FAO occurs during prolonged fasting and/or periods of increased energy demands (fever, stress, and common infections) when energy production relies increasingly on fat metabolism. These disorders have wide clinical variability.

You Should Take the Following IMMEDIATE Actions:

- Inform family of the newborn screening result
- Ascertain clinical status (poor feeding, vomiting, lethargy, odor of sweaty feet, respiratory distress).
- Consult with pediatric metabolic specialist the same day.
- Evaluate the newborn for signs of failure to thrive, lethargy, hypoketotic hypoglycemia, metabolic acidosis, hyperammonemia, odor of sweaty feet, and/or facial dysmorphism. If any of these findings are present or if the newborn is ill, transport to a hospital for further treatment in consultation with the metabolic specialist.
- Initiate confirmatory/diagnostic testing and management as recommended by the specialist.
- Provide family with basic information about GA-II, including management.

- Report final diagnostic outcome to newborn screening program.

Diagnostic Evaluation: Plasma acylcarnitines: acylcarnitines including C4, C5, and C8 are characteristically elevated in GA-II. C4 (+/- C5) is elevated in EE. Urine organic acids: GA-II patients have a complex pattern including elevated glutaric and 2-hydroxyglutaric acids and multiple fatty acid metabolites. EE is associated with elevated ethylmalonic acid with mild elevations of glycine conjugates including isovalerylglycine. Urine acylglycines demonstrate characteristic abnormalities of either GA-II or EE. Molecular genetic testing may be required to confirm and differentiate the diagnoses.

Clinical Considerations: The clinical spectrum of GA-II presents from infancy to adulthood with muscle weakness, exercise intolerance, and/or muscle pain. Affected newborns may demonstrate lethargy, poor feeding and facial dysmorphisms with metabolic acidosis and hypoketotic hypoglycemia and hyperammonemia. Treatment includes the avoidance of fasting and supplementation with riboflavin, L-carnitine, and coenzyme Q10. EE can present in infancy with developmental delay, diarrhea, and petechiae. RMD are a group of rare neurologic conditions clinically similar to GA-II except Riboflavin Transporter Deficiency (RTD) which is characterized by progressive peripheral and cranial neuropathy causing muscle weakness, vision loss, deafness, and sensory ataxia. High dose supplementation with riboflavin may be life saving for these disorders.

Additional Information:

How to Communicate Newborn Screening Results
GARD (GA II | RTD (RMD))
Gene Reviews (GA II | RTD (RMD) | EE | MADD)
Medline Plus (GA II | RTD (RMD))
Condition Information for Families- HRSA Newborn Screening Clearinghouse

Referral (local, state, regional, and national):

[Find a Genetics Clinic Directory]
[Genetic Testing Registry]

Local Resources *(Insert Local Website Links)*

State Resource Site (Insert Website Information)

Name	
URL	
Comments	

Local Resource Site (Insert Website Information)

Name	
URL	
Comments	

Appendix *(Resources with Full URL Addresses)*

Additional Information

How to Communicate Newborn Screening Results

- https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/resources/achdnc-communication-guide-newborn.pdf

GARD

- https://rarediseases.info.nih.gov/diseases/6523/glutaric-acidemia-type-ii
- https://rarediseases.info.nih.gov/diseases/9993/riboflavin-transporter

Gene Reviews

- https://www.ncbi.nlm.nih.gov/books/NBK558236/
- https://www.ncbi.nlm.nih.gov/books/NBK299312/
- https://www.ncbi.nlm.nih.gov/books/NBK453432/
- https://www.ncbi.nlm.nih.gov/books/NBK558236/

Medline Plus

- https://medlineplus.gov/genetics/condition/glutaric-acidemia-type-ii
- https://medlineplus.gov/genetics/condition/riboflavin-transporter-deficiency-neuronopathy/

Condition Information for Families-HRSA Newborn Screening Clearinghouse

- https://newbornscreening.hrsa.gov/conditions/glutaric-acidemia-type-ii

Referral (local, state, regional and national)

Find a Genetics Clinic Directory

- https://clinics.acmg.net

Genetic Testing Registry

- https://www.ncbi.nlm.nih.gov/gtr/