

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 <u>IMMEDIATE</u> 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: <u>Plasma acylcarnitines:</u> acylcarnitines including C4, C5, and C8 are characteristically elevated in GA-II. C4 (+/- C5) is elevated in EE. <u>Urine organic acids:</u> 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. <u>Urine acylglycines</u> demonstrate characteristic abnormalities of either GA-II or EE. <u>Molecular genetic testing</u> 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

This practice resource is designed primarily as an educational resource for medical geneticists and other clinicians to help them provide quality medical services. Adherence to this practice resource is completely voluntary and does not necessarily assure a successful medical outcome. This practice resource should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this practice resource. Clinicians also are advised to take notice of the date this practice resource was adopted, and to consider other medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

© American College of Medical Genetics and Genomics, 2022 Content Updated: September 2022 (Funded in part through MCHB/HRSA/HHS grant #U22MC03957; National Coordinating Center for the Regional Genetics Networks)



ACT Sheet

Referral (local, state, regional, and national): <u>Find a Genetics Clinic Directory</u> <u>Genetic Testing Registry</u>

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/achdnccommunication-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

• <u>https://clinics.acmg.net</u>

- Genetic Testing Registry
 - <u>https://www.ncbi.nlm.nih.gov/gtr/</u>

This practice resource is designed primarily as an educational resource for medical geneticists and other clinicians to help them provide quality medical services. Adherence to this practice resource is completely voluntary and does not necessarily assure a successful medical outcome. This practice resource should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this practice resource. Clinicians also are advised to take notice of the date this practice resource was adopted, and to consider other medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

© American College of Medical Genetics and Genomics, 2022 Content Updated: September 2022 (Funded in part through MCHB/HRSA/HHS grant #U22MC03957; National Coordinating Center for the Regional Genetics Networks)