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

ACT Sheet

Newborn Screening ACT Sheet

[Decreased Citrulline]

Differential Diagnosis: Ornithine transcarbamylase (OTC) deficiency; carbamoyl phosphate synthetase 1 (CPS) deficiency; N-acetylglutamate synthetase (NAGS) deficiency; MT-ATP6 related mitochondrial disease.

Condition Description: Decreased citrulline can result from a defect early in the urea cycle, the pathway that converts ammonia to urea. Deficiencies in OTC, CPS, and NAGS all cause decreased citrulline and hyperammonemia, which can be severe and life-threatening. OTC deficiency is distinguished from the other disorders by elevated orotic acid, and by X-linked inheritance.

You Should Take the Following IMMEDIATE Actions:

- Inform family of the newborn screening result.
- Ascertain clinical status (poor feeding, vomiting, lethargy, tachypnea).
- Consult the pediatric metabolic specialist the same day.
- Evaluate the newborn (poor feeding, vomiting, lethargy, hypotonia, tachypnea, seizures, signs of liver disease) and obtain an ammonia level immediately. If any of these signs 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 information about the possible diagnoses and their management.

- Report final diagnostic outcome to the newborn screening program.

Diagnostic Evaluation: Plasma ammonia will demonstrate hyperammonemia when present. Plasma amino acids: Citrulline is decreased in all four deficiencies (OTC, CPS, NAGS, MT-ATP6). Urine organic acids or quantitative orotic acid: Orotic acid is only elevated in OTC deficiency, and is more readily detected by the quantitative test. Plasma acylcarnitine profile: C3 and/or C5-OH acylcarnitines can be elevated in MT-ATP6 deficiency. Molecular genetic testing can distinguish these disorders and is often required to confirm the diagnoses.

Clinical Considerations: OTC, CPS and NAGS deficiencies can present acutely in the newborn period with hyperammonemia, respiratory alkalosis, seizures, vomiting, lethargy, and coma. Females with OTC deficiency may become symptomatic, with some developing hyperammonemia during intercurrent illness or with other stressors. Later signs include recurrent hyperammonemia with illness or with fasting, and intellectual disability. MT-ATP6 related mitochondrial disease in infants with low citrulline and elevated C5-OH levels have been associated with Leigh syndrome, a neurodegenerative disorder. Treatment specific for each disorder can lead to optimized growth and development and may be lifesaving.

Additional Information:

How to Communicate Newborn Screening Results
Emergency Protocols (New England Consortium of Metabolic Programs)
Gene Reviews (OTC Deficiency | MT-ATP6-related mitochondrial disease/Leigh syndrome)
Medline Plus (OTC Deficiency | CPS Deficiency | NAGS Deficiency | CAVA Deficiency | MT-ATP6-related mitochondrial disease/Leigh syndrome)
Condition Information for Families- HRSA Newborn Screening Clearinghouse (OTC Deficiency | CPS Deficiency)

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

Find a Genetics Clinic Directory
Genetic Testing Registry

 (Funded in part through MCHB/HRSA/HHS grant #U22MC03957;#UH9MC30770; National Coordinating Center for the Regional Genetics Networks)

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

Emergency Protocols (New England Consortium of Metabolic Programs)

- https://www.newenglandconsortium.org/neonateinfantchild-with-hyperammonemia

Gene Reviews

- https://www.ncbi.nlm.nih.gov/books/NBK154378/
- https://www.ncbi.nlm.nih.gov/books/NBK1173/

Medline Plus

- OTC Deficiency
  - https://medlineplus.gov/genetics/condition/ornithine-transcarbamylase-deficiency/
- CPS Deficiency
  - https://medlineplus.gov/genetics/condition/carbamoyl-phosphate-synthetase-i-deficiency/
- NAGS Deficiency
  - https://medlineplus.gov/genetics/condition/n-acetylglutamate-synthase-deficiency/
- CAVA Deficiency
  - https://medlineplus.gov/genetics/condition/carbonic-anhydrase-va-deficiency/
- MT-ATP6-related mitochondrial disease/Leigh syndrome
  - https://medlineplus.gov/genetics/condition/leigh-syndrome/

Condition Information for Families-HRSA Newborn Screening Clearinghouse

- OTC Deficiency
  - https://newbornscreening.hrsa.gov/conditions/ornithine-transcarbamylase-deficiency
- CPS Deficiency
  - https://newbornscreening.hrsa.gov/conditions/carbamoyl-phosphate-synthetase-i-deficiency

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/