

American College of Medical Genetics and Genomics

Newborn Screening ACT Sheet

[Elevated C5-OH Acylcarnitine]

Organic Acidemias

Differential Diagnosis: 3-methylcrotonyl-CoA carboxylase (MCC) deficiency, maternal MCC deficiency, 3-hydroxy-3methylglutaryl-CoA lyase (HMG) deficiency; **B-ketothiolase (BKT) deficiency**; multiple carboxylase deficiency (MCD) (holocarboxylase synthetase deficiency [HCS] or biotinidase deficiency [BTD]), 2-methyl-3-hydroxybutyric acidemia (MHBD), 3-methylglutaconic aciduria (MGA), and MT-ATP6 related mitochondrial disorders.

Condition Description: Elevated C5-OH is associated with a group of organic acid disorders caused by a deficiency of an enzyme involved in the catabolism of branched chain amino acids. In most of the disorders, potentially toxic metabolites accumulate with variable clinical presentations. Each of the disorders is caused by a deficiency of the relevant enzyme. Of these disorders, MCC deficiency is the most common. HMG and HCS deficiencies can present acutely in the neonatal period.

You Should Take the Following <u>IMMEDIATE</u> Actions:

- Inform family of the newborn screening result.
- Ascertain clinical status (poor feeding, vomiting, lethargy).
- Consult with pediatric metabolic specialist the same day.
- Evaluate the newborn (hypoglycemia, ketonuria, metabolic acidosis). 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 as recommended by the specialist.
- Provide the family with basic information about the possible diagnoses and their management, including the need for urgent treatment of metabolic acidosis.
- Report final diagnostic outcome to newborn screening program.

Diagnostic Evaluation: <u>Plasma acylcarnitine profile:</u> C5-OH is elevated in all conditions; C5:1 (tiglylcarnitine) is also elevated in BKT deficiency. <u>Urine organic acids</u> demonstrate abnormal patterns characteristic of each condition. <u>Urine organic acids</u> and <u>plasma acylcarnitines</u> performed on infant and mother *are* warranted to evaluate for maternal MCC deficiency. <u>Serum biotinidase</u>: identifies biotinidase deficiency. <u>Plasma amino acids</u>: may demonstrate reduced citrulline in MT-ATP6-related disorders. <u>Enzymatic and molecular genetic testing</u> may be required.

Clinical Considerations: MCC deficiency is the most common of these disorders and most individuals with this diagnosis remain asymptomatic. Neonates with HMG and HCS deficiencies can present acutely with feeding difficulties, hypotonia, lethargy, and seizures; avoidance of fasting in these neonates is essential. Clinical features vary among the other conditions and can include episodes of hypoglycemia, lethargy, and hypotonia occurring during infancy and/or childhood. MGA comprises a heterogenous group of disorders associated with diminished mitochondrial function. MT-ATP6-related mitochondrial disorders have been associated with Leigh syndrome, a neurodegenerative disorder. There is treatment available that is specific to each condition.

Additional Information:

How to Communicate Newborn Screening Results

Emergency Protocols (New England Consortium of Metabolic Programs) (HMG | MCC) Gene Reviews (BTD) Medline Plus (HMG | MCC | BKT | HCS | BTD | MGA | MT-ATP6-related mitochondrial disease/Leigh syndrome) Condition Information for Families- HRSA Newborn Screening Clearinghouse (HMG | MCC | BKT | MCD | HCS | BTD | MGA)

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

Find a Genetics Clinic Directory Genetic Testing Registry

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.

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ACT Sheet

[Elevated C5-OH Acylcarnitine] ß-ketothiolase (BKT) deficiency

State and Other Resources

State Newborn Screening Program

Metabolic (Bloodspot) Screening, Montana's Newborn Screening Programs 406-444-0984, dphhs.mt.gov/ecfsd/cshs/newbornscreeningprograms/

Short-term Follow-up Coordinator - Crystal Fortune, MT Laboratory Services Bureau 406-444-0930 or 800-821-7284 cfortune@mt.gov

Genetics/Metabolics Consultants

Shodair Children's Hospital Medical Genetics Staff will contact you with recommendations. Metabolic Clinic: 406-444-1099; Clinics held across Montana: 406-444-1016 shodair.org/about-shodair/contact/

If emergency consultation with a metabolic specialist is necessary, contact One Call (24/7) at Children's Hospital Colorado (800-525-4871) and ask to speak to the metabolic specialist on call.

Information for Clinicians and Families

Montana Medical Home Portal (see Newborn Disorders and Parents & Families sections) mt.medicalhomeportal.org/newborn/beta-ketothiolase-deficiency

Parent/Family Support

Organic Acidemia Association http://www.oaanews.org/bkt.html

National Resources (with web addresses)

Additional Information

How to Communicate Newborn Screening Results www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/Resources/achdnccommunication-guide-newborn.pdf

GARD (Genetic and Rare Diseases Information Center) rarediseases.info.nih.gov/diseases/872/beta-ketothiolase-deficiency

Medline Plus medlineplus.gov/genetics/condition/beta-ketothiolase-deficiency/

Condition Information for Families-HRSA Newborn Screening Clearinghouse newbornscreening.hrsa.gov/conditions/beta-ketothiolase-deficiency

Referral (local, state, regional and national)

Find a Genetics Clinic Directory clinics.acmg.net

Genetic Testing Registry www.ncbi.nlm.nih.gov/gtr/

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