

Absent/Reduced Biotinidase Activity

Biotinidase Deficiency

Differential Diagnosis: Biotinidase deficiency; see C5-OH for non-biotinidase associated conditions.

Metabolic Description: Biotinidase deficiency results from defective activity of the biotinidase enzyme. When identified (possibly) through elevated C5-OH, 3-hydroxyisovaleric acid and 3-methylcrotonylglycine are elevated, and holocarboxylase synthase deficiency must be considered.

You Should Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, lethargy, hypotonia).
- ◆ See and evaluate infant.
- ◆ Consultation/referral to a metabolic specialist to determine appropriate follow-up. (See attached list.)
- ◆ If infant cannot be seen immediately by a metabolic specialist, undertake confirmatory testing in consultation with a metabolic specialist.
- ◆ Initial testing: enzyme assay for biotinidase.
- ◆ Repeat newborn screen if second screen has not been done.
- ◆ Begin emergency treatment if symptomatic.
- ◆ Report findings to newborn screening program.

Confirmation of Diagnosis: Enzyme assay for biotinidase reveals low activity. Plasma acylcarnitine analysis may show normal or increased 3-hydroxyisovaleric acid and 3-methylcrotonylglycine. C5-OH acylcarnitine may be high, but lack of an abnormal acylcarnitine profile does not rule out biotinidase deficiency.

Clinical Expectations: The neonate is usually asymptomatic, but episodic hypoglycemia, lethargy, hypotonia, and mild developmental delay can occur at any time from the neonatal period through childhood. Untreated biotinidase deficiency leads to developmental delay, seizures, alopecia, and hearing deficits. Biotin treatment is available and highly effective.

Reporting: Report diagnostic result to family and NBS program.

Additional Information:

Gene Tests

<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=EJ4Gy2VAan2GT&gry=&fcn=y&fw=xn8V&filena me=/profiles/biotin/index.html>

OMIM

<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=253260>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=biotinidasedeficiency>

Elevated 17-Hydroxyprogesterone (17-OHP)

Congenital Adrenal Hyperplasia (CAH)

Differential Diagnosis: Congenital Adrenal Hyperplasia (CAH), 21-OH deficiency, stress, or prematurity are possible secondary causes of increased 17-OHP.

Condition Description: Lack of adequate adrenal cortisol and aldosterone, and increased androgen production.

Medical Emergency: Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status.
- ◆ Consult with pediatric endocrinologist, having the following information available (sex, age at NBS sampling, birth weight) and refer, if needed.
- ◆ Examine the newborn (ambiguous genitalia or non-palpable testes, lethargy, vomiting, poor feeding).
- ◆ Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- ◆ Initial testing: serum electrolytes, 17-OHP.
- ◆ Repeat the newborn screen if the second screen has not been done.
- ◆ Emergency treatment as indicated (e.g., IV fluids, IM/IV hydrocortisone).
- ◆ Educate family about signs, symptoms, and need for urgent treatment of adrenal crisis.
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Diagnostic tests include serum 17-OHP (increased), serum electrolytes (reduced sodium and increased potassium), and blood glucose (reduced). Additional tests may be recommended by the specialist.

Clinical Expectations: Ambiguous genitalia in females who may appear to be male with non-palpable testes. At risk for life threatening adrenal crises, shock, and death in males and females. Finding could also be a false positive associated with stress or prematurity.

Additional Information:

Gene Tests/Gene Clinics

<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=PDqbsAPHeqXyl&gry=&fcn=y&fw=mhZr&filena me=/profiles/cah/index.html>

Cares Foundation

<http://caresfoundation.org>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=21hydroxylasedeficiency>

Increased Citrulline

Amino Aciduria/Urea Cycle Disorder

Differential Diagnosis: Citrullinemia I, argininosuccinic acidemia; citrullinemia II (citrin deficiency), pyruvate carboxylase deficiency.

Condition Description: The urea cycle is the enzyme cycle whereby ammonia is converted to urea. In citrullinemia and in argininosuccinic acidemia, defects in ASA synthetase and lyase, respectively, in the urea cycle result in hyperammonemia and elevated citrulline.

Medical Emergency: Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, tachypnea).
- ◆ Immediately consult with pediatric metabolic specialist. (See attached list.)
- ◆ Evaluate the newborn (poor feeding, vomiting, lethargy, hypotonia, tachypnea, seizures and signs of liver disease). Measure blood ammonia.
- ◆ If any sign is present or infant is ill, initiate emergency treatment for hyperammonemia in consultation with metabolic specialist.
- ◆ Transport to hospital for further treatment in consultation with metabolic specialist.
- ◆ Initiate timely confirmatory/diagnostic testing and management, as recommended by specialist.
- ◆ Initial testing: plasma quantitative amino acids.
- ◆ Repeat newborn screen if second screen has not been done.
- ◆ Provide family with basic information about hyperammonemia.
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Plasma ammonia to determine presence of hyperammonemia. In citrullinemia, plasma amino acid analysis will show increased citrulline, whereas in argininosuccinic acidemia, argininosuccinic acid will also be present. Orotic acid may be increased in both disorders, which can be determined by urine organic acid analysis. In citrin deficiency, liver enzymes, lactic acid and bilirubin may be elevated. For pyruvate carboxylase deficiency, blood lactate and pyruvate will be elevated.

Clinical Considerations: Citrullinemia and argininosuccinic acidemia can present acutely in the newborn period with hyperammonemia, seizures, failure to thrive, lethargy, and coma. Later signs include mental retardation. Citrin deficiency may present with cholestatic liver disease in the newborn period. Pyruvate carboxylase deficiency produces coma seizures and life-threatening ketoacidosis. Treatment for ASA and citrullinemia is to promote normal growth and development and to prevent hyperammonemia.

Additional Information:

Gene Tests/Gene Clinics

<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=HWrct-uSqlup&gry=&fcn=y&fw=b8Mv&filename=/profiles/ctlm/index.html>

Star G FELSI

<http://www.newbornscreening.info/Pro/aminoacid disorders/ASAS.html>
<http://www.newbornscreening.info/Parents/aminoacid disorders/ASAS.html>
<http://www.newbornscreening.info/Parents/aminoacid disorders/ASAL.html>
<http://www.newbornscreening.info/Pro/aminoacid disorders/ASAL.html>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=citrullinemia>

Elevated C0/C16+C18

Carnitine Palmitoyl Transferase 1 Deficiency (CPT1)

Differential Diagnosis: Carnitine palmitoyl transferase 1 deficiency (CPT1).

Condition Description: This disorder is caused by a deficiency of the enzyme CPT1, preventing the fatty acid carnitine-acylcarnitine linkage required to transport fatty acids into the mitochondria. This results in accumulation of free carnitine (C0) and prevents the fatty acid oxidation response necessary to generate energy during fasting and increased energy needs (fever, stress).

Medical Emergency: Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status (lethargy, seizures).
- ◆ Consult with pediatric metabolic specialist. (See attached list.)
- ◆ Evaluate the newborn (lethargy, hepatomegaly, seizures).
- ◆ Initiate emergency treatment as indicated by metabolic specialist.
- ◆ Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- ◆ Initial testing: plasma carnitine, plasma acylcarnitine analysis.
- ◆ Repeat newborn screen if second screen has not been done.
- ◆ Educate family about signs, symptoms and need for urgent treatment of hypoglycemia (lethargy, seizures).
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Plasma acylcarnitine showing elevated free carnitine C0 with low or normal long-chain acylcarnitines. CPT1 enzyme assays and CPT1A gene sequencing establish the diagnosis.

Clinical Considerations: CPT1A can have a variable presentation. Critical hypoketotic hypoglycemia is a common presenting feature. Newborns may appear asymptomatic, but can progress to fasting hypoketotic hypoglycemia, lethargy, hepatomegaly, and seizures, usually precipitated by fasting or acute illness.

Additional Information:

Gene Reviews

<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=8dyMD9leb4zcn&gry=&fcn=y&fw=cqEF&filename=/profiles/cpt1a/index.html>

Genetics Home Reference

<http://ghr.nlm.nih.gov/gene=cpt1a>

STAR-G/HRSA

<http://www.newbornscreening.info/Parents/fattyaciddisorders/CPT1.html>

Decreased C0 and Other Acylcarnitines

Carnitine Uptake Defect (CUD)

Differential Diagnosis: Carnitine uptake defect (CUD).

Condition Description: CUD is caused by a defect in the carnitine transporter that moves carnitine across the plasma membrane. Reduced carnitine limits acylcarnitine formation preventing transport of fatty acids into mitochondria, thereby limiting energy production. Tissues with high energy needs (skeletal and heart muscle) are particularly affected.

Medical Emergency: Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, lethargy, tachypnea).
- ◆ Consult with pediatric metabolic specialist. (See attached list.)
- ◆ Evaluate the newborn (tachycardia, hepatomegaly, reduced muscle tone).
- ◆ Initiate emergency treatment as indicated by metabolic specialist.
- ◆ Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- ◆ Initial testing: (free and total) plasma carnitine and urine carnitine.
- ◆ Repeat newborn screen if the second screen has not been done.
- ◆ Educate family about signs, symptoms, and need for urgent treatment if infant becomes ill.
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Plasma and urine carnitine analysis will reveal decreased free and total carnitine (C0) in plasma and overexcretion of carnitine in urine. The newborn's mother should be investigated, as well, because several cases of maternal CUD have been identified following an abnormal newborn screening result in their offspring. Transporter assays and OCTN2 gene sequencing establish the diagnosis.

Clinical Considerations: Carnitine transporter defect has a variable expression and variable age of onset. Characteristic manifestations include lethargy, hypotonia, hepatomegaly, and cardiac decompensation due to cardiomyopathy. Hypoglycemia is typical in acute episodes.

Additional Information:

OMIM

<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=212140>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=primarycarnitinedeficiency>

STAR-G/HRSA

<http://www.newbornscreening.info/Parents/fattyacid disorders/Carnitine.html> <http://www.newbornscreening.info/Pro/fattyacid disorders/Ctd.html>

Elevated C5-OH Acylcarnitine Organic Acidemias

Differential Diagnosis: Most likely 3-methylcrotonyl-CoA carboxylase (3MCC) deficiency (infant or mother); may be 3-hydroxy-3-methylglutaryl (HMG)-CoA lyase deficiency; β -ketothiolase deficiency (BKT); multiple carboxylase deficiency (MCD), including biotinidase deficiency and holocarboxylase deficiency, 2-methyl-3-hydroxybutyric acidemia (2M3HBA), 3-methylglutaconic aciduria (3MGA).

Condition Description: Each of the disorders is caused by a deficiency of the relevant enzyme. The substrate, for which the enzyme is named, accumulates as does its potentially toxic metabolites in most of the disorders.

Medical Emergency: Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).
- ◆ Consult with pediatric metabolic specialist. (See attached list.)
- ◆ Evaluate the newborn (hypoglycemia, ketonuria, metabolic acidosis).
- ◆ If any of these parameters are abnormal or the infant is ill, initiate emergency treatment as indicated by metabolic specialist and transport IMMEDIATELY to tertiary center with metabolic specialist.
- ◆ Initial testing: urine organic acids, plasma acylcarnitine analysis. Acylcarnitine profile on mother.
- ◆ Repeat newborn screen if second screen has not been done.
- ◆ Educate family about signs, symptoms, and need for urgent treatment of metabolic acidosis (poor feeding, vomiting, lethargy).
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Confirmatory tests include urine organic acids on infant and mother, plasma acylcarnitine analysis, and serum biotinidase assay. The organic acids analysis on infant and mother should clarify the differential, except for holocarboxylase deficiency and biotinidase deficiency (the latter clarified by biotinidase assay).

Clinical Considerations: The neonate is usually asymptomatic in 3MCC deficiency. However, episodic hypoglycemia, lethargy, hypotonia, and mild developmental delay can occur at any time from the neonatal period through childhood for any of these disorders. There is beneficial treatment that is specialized to each condition.

Additional Information:

Emergency Treatment Protocol

http://www.childrenshospital.org/newenglandconsortium/NBS/Emergency_Protocols.html

3MCC

<http://www.childrenshospital.org/newenglandconsortium/NBS/MMC.html>

HMG CoA lyase deficiency

<http://www.childrenshospital.org/newenglandconsortium/NBS/HMG.html>

STAR-G/HRSA

<http://www.newbornscreening.info/Parents/facts.html>
<http://www.newbornscreening.info/Pro/facts.html>

Gene Clinics <http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888892&key=yedaVhVZIR6qb&gry=&fcn=y&fw=dns7&filename=/profiles/oa-overview/index.html>

Genetics Home Reference

3MCC <http://ghr.nlm.nih.gov/condition=3methylcrotonylcoacarbonylasedeficiency>

Holocarboxylase synthetase deficiency <http://ghr.nlm.nih.gov/condition=holocarboxylasesynthetasedeficiency>

HMG CoA lyase deficiency <http://ghr.nlm.nih.gov/condition=3hydroxy3methylglutarylcoalyasedeficiency>

BKT <http://ghr.nlm.nih.gov/condition=betaketothiolasedeficiency>

Elevated C5-DC Acylcarnitine Glutaryl-CoA Dehydrogenase Deficiency

Differential Diagnosis: Glutaric aciduria (GA-1)

Condition Description: GA-I is caused by a defect of glutaryl-CoA dehydrogenase, which limits the metabolism of glutaryl-CoA to crotonyl-CoA, resulting in increased glutaric acid (toxic) and its metabolites.

You Should Take the Following Actions

- ◆ **Contact family IMMEDIATELY to inform them of the newborn screening result.**
- ◆ **Consult with pediatric metabolic specialist. (See attached list.)**
- ◆ **Evaluate the newborn for macrocephaly and muscle hypotonia; initiate confirmatory/ diagnostic testing as recommended by metabolic specialist.**
- ◆ **Initial testing: Plasma acylcarnitine profile, urine organic acids.**
- ◆ **Repeat newborn screen if the second screen has not been done.**
- ◆ **Refer to metabolic specialist to be seen as soon as possible – not any later than three weeks.**
- ◆ **Educate family about diagnostic possibilities, complexity of diagnostic work-up, and the possibility of neurodegenerative crisis with an intercurrent infectious illness.**
- ◆ **IMMEDIATE treatment with IV glucose is needed for intercurrent infectious illness.**
- ◆ **Report findings to newborn screening program.**

Diagnostic Evaluation: Urine organic acid analysis will reveal elevated glutaric acid, and 3-hydroxyglutaric acid should be ordered promptly and is often diagnostic. If urine organic acids don't confirm the diagnosis, the metabolic specialist will consider analyzing glutarylcarnitine in urine and 3-hydroxyglutaric acid in blood and CSF, enzyme assay in fibroblasts, and molecular analysis of the GCDH gene.

Clinical Considerations: The neonate with glutaric acidemia type I is usually macrocephalic, but otherwise asymptomatic. Later signs include metabolic ketoacidosis, failure to thrive, and sudden onset of dystonia and athetosis due to irreversible striatal damage. With appropriate treatment, 60-70% of patients will not suffer neurodegenerative disease.

Additional Information:

New England Metabolic Consortium

<http://www.childrenshospital.org/newenglandconsortium/NBS/descriptions/GA1.html>

Gene Tests/Gene Clinics

<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=NexQvDbtfnPSK&gry=&fcn=y&fw=UOcs&filena me=/profiles/oa-overview/index.html>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=glutaricacidemiatypei>

STAR G FELSI

<http://www.newbornscreening.info/Pro/organicaciddisorders/GA1.html>

<http://www.newbornscreening.info/Parents/organicaciddisorders/GA1.html>

Absent/Reduced Galactose-1-phosphate Uridyltransferase (GALT)

Classical Galactosemia

Differential Diagnosis: Galactosemia (galactose-1-phosphate uridyltransferase deficiency); GALT heterozygotes; GALT variants; artifactual reductions due to enzyme inactivation by high temperature and/or humidity.

Condition Description: In galactosemia, GALT deficiency results in accumulation of galactose-1-phosphate (Gal-1-P), and galactose, causing multiorgan disease.

Medical Emergency: Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result, ascertain clinical status, arrange immediate clinical evaluation, stop breast or cow's milk, and initiate non-lactose feeding (powder-based soy formula).
- ◆ Consult with metabolic specialist; refer if considered appropriate.
- ◆ Evaluate the infant (jaundice, poor feeding, vomiting, lethargy, bulging fontanel, and bleeding), and arrange diagnostic testing as directed by metabolic specialist.
- ◆ Initiate emergency treatment as recommended by metabolic specialist. If baby is sick, admit to hospital.
- ◆ Repeat newborn screen if second screen has not yet been done.
- ◆ Educate family about importance of diet change.
- ◆ Report findings to newborn screening program.

Confirmation of Diagnosis: Quantification of erythrocyte galactose-1-phosphate (gal-1-P) and GALT. Classical galactosemia shows <1% GALT activity and markedly increased gal-1-P.

Transfusions in infant can invalidate the results of erythrocyte enzyme assays. Enzyme variants may be distinguished by GALT electrophoresis or mutation analysis.

Clinical Considerations: Classical galactosemia presents in the first few days of life and may be fatal without treatment. Signs include poor feeding, vomiting, jaundice and, sometimes, lethargy and/or bleeding. Neonatal E. coli sepsis can occur and is often FATAL. Treatment is withdrawal of milk and, if symptomatic, emergency measures.

Additional Information:

New England Metabolic Consortium

http://www.childrenshospital.org/newenglandconsortium/NBS/gal/gal_protocol.htm

Gene Tests/Gene Clinics

<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=0JvJTPALRrmnH&gry=&fcn=y&fw=SCnL&filena me=/profiles/galactosemia/index.html>

Genetics Home Reference

<http://ghr.nlm.nih.gov/ghr/search;jsessionid=289977E2FEE78964E00123B56DB1E569?query=galactosemia>

FS (HbSS Disease or HbS/Beta Zero Thalassemia) Sickle Cell Anemia

Differential Diagnosis: Homozygous sickle cell disease (Hb SS), sickle beta-zero thalassemia, or sickle hereditary persistence of fetal hemoglobin (S-HPFH).

Condition Description: A red blood cell disorder characterized by presence of fetal hemoglobin (F) and hemoglobin S in the absence of hemoglobin A. The hemoglobins are listed in order of the amount of hemoglobin present (F>S). This result is different from FAS, which is consistent with sickle carrier.

You Should Take the Following Actions

- ◆ Contact the family to inform them of the screening result.
- ◆ Consult a specialist in hemoglobinopathies; refer if needed. (See attached list.)
- ◆ Evaluate infant and assess for splenomegaly.
- ◆ Repeat newborn screen if second screen has not yet been done.
- ◆ Initiate daily penicillin VK (125mg po bid) prophylaxis and other treatment as recommended by the consultant.
- ◆ Educate parents/caregivers regarding the risk of sepsis, the need for urgent evaluation if fever of $\geq 38.5^{\circ}\text{C}$ (101°F), or signs and symptoms of splenic sequestration.
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Hemoglobin separation by electrophoresis, isoelectric focusing or HPLC showing FS pattern. Family or DNA studies may be used to confirm genotype. Sickledex is not appropriate for confirmation of diagnosis in infants.

Clinical Considerations: Newborn infants are usually well. Hemolytic anemia and vaso-occlusive complications develop during infancy or early childhood. Complications include life-threatening infection, splenic sequestration, pneumonia, acute chest syndrome, pain episodes, aplastic crisis, dactylitis, priapism, and stroke. Comprehensive care, including family education, immunizations, prophylactic penicillin, and prompt treatment of acute illness, reduces morbidity and mortality. S-HPFH is typically benign.

Additional Information:

Grady Comprehensive Sickle Cell Center
<http://scinfo.org/hemoglb.htm#SICKLE%20HEMOGLOBINS>

Management and Therapy of Sickle Cell Disease
<http://www.nhlbi.nih.gov/health/prof/blood/sickle/index.htm>

Sickle Cell Disease in Children and Adolescents: Diagnosis, Guidelines for Comprehensive Care, and Care Paths and Protocols for Management of Acute and Chronic Complications
http://www.dshs.state.tx.us/newborn/sc_guide.htm

American Academy of Pediatrics
<http://pediatrics.aappublications.org/cgi/content/full/109/3/526>

Sickle Cell Disease Association
<http://www.sicklecelldisease.org>

Comprehensive Sickle Cell Center Directory
<http://www.rhofed.com/sickle/index.htm>

Sickle Cell Information Center
<http://www.scinfo.org/clinics.htm>

[FSA]

Hemoglobin S/Beta⁺Thalassemia (HbSβ⁺ Disease)

Differential Diagnosis: Hemoglobin FSA pattern on newborn screen is highly suggestive of sickle beta plus thalassemia. The hemoglobins are listed in order (F>S>A) of the amount of hemoglobin present. This result is different from FAS, which is consistent with sickle carrier (trait).

Condition Description: Individuals with sickle beta⁺ thalassemia, a form of sickle cell disease, are compound heterozygotes for the Hb S and beta-thalassemia mutations in the beta-globin genes.

You Should Take the Following Actions

- ◆ Contact the family to inform them of the screening result.
- ◆ Perform a physical exam on the infant and assess for splenomegaly.
- ◆ Repeat newborn screen if second screen has not yet been done.
- ◆ Initiate penicillin (PenVK 125mg po bid) prophylaxis.
- ◆ Educate parents/caretakers regarding the risk of sepsis and advise that infant be immediately evaluated if a fever of $\geq 38.5^{\circ}\text{C}$ (101°F) is present.
- ◆ Contact a specialist in hemoglobinopathies for consultation on diagnostic evaluation and management. (See attached list.)
- ◆ Report findings to newborn screening program.

Confirmation of Diagnosis: Hemoglobin separation by electrophoresis, isoelectric focusing, or HPLC showing FSA. Family or DNA studies may be used to confirm genotype.

Clinical Expectations: Infants are usually normal at birth. Later potential clinical problems include mild hemolytic anemia, life-threatening infection, vaso-occlusive pain episodes, dactylitis, and chronic organ damage. Prompt treatment of infection and splenic sequestration is associated with decreased mortality in the first three years of life.

Additional Information:

Grady Comprehensive Sickle Cell Center <http://scinfo.org/hemoglb.htm#SICKLE%20HEMOGLOBINS> <http://www.scinfo.org/hemoglb.htm#BETA%20THALASSEMIAS>

Management and Therapy of Sickle Cell Disease
<http://www.nhlbi.nih.gov/health/prof/blood/sickle/index.htm>

Sickle Cell Disease in Children and Adolescents: Diagnosis, Guidelines for Comprehensive Care, and Protocols for Management of Acute and Chronic Complications
<http://www.dshs.state.tx.us/newborn/pdf/sedona02.pdf>

American Academy of Pediatrics
<http://pediatrics.aappublications.org/cgi/content/full/109/3/526>

Sickle Cell Disease Association of America
<http://sicklecelldisease.org/>

Referral (local, state, regional and national): Comprehensive Sickle Cell Center Directory
<http://www.rhofed.com/sickle/index.htm>

Sickle Cell Information Center
<http://www.scinfo.org/clinics.htm>

Newborn Screening ACT Sheet

[FSC]

Hemoglobin SC Disease (HbSC)

Differential Diagnosis: Hemoglobin SC disease most likely.

Condition Description: A red cell disorder characterized by the presence of fetal hemoglobin (F) and hemoglobins S and C in the absence of Hb A. The hemoglobins are listed in order of the amount of hemoglobin present (F>S>C). This result is different from FAS, which is consistent with sickle carrier.

You Should Take the Following Actions

- ◆ Contact the family to inform them of the screening result.
- ◆ Consult a specialist in hemoglobinopathies; refer if needed. (See attached list.)
- ◆ Evaluate infant and assess for splenomegaly.
- ◆ Repeat newborn screen if second screen has not yet been done.
- ◆ Initiate timely confirmatory/diagnostic testing as recommended by consultant.
- ◆ Initiate treatment as recommended by the consultant.
- ◆ Educate parents/caregivers regarding the risk of sepsis, the need for urgent evaluation for fever of $\geq 38.5^{\circ}\text{C}$ (101°F), and signs and symptoms of splenic sequestration.
- ◆ Report findings to newborn screening program.

Confirmation of Diagnosis: Hemoglobin separation by electrophoresis, isoelectric focusing, or HPLC showing FSC. Family or DNA studies may be used to confirm genotype.

Clinical Expectations: Newborn infants are usually well. Hemolytic anemia and vaso-occlusive complications develop during infancy or early childhood. Complications include life-threatening infection, splenic sequestration, pneumonia, acute chest syndrome, pain episodes, aplastic crisis, dactylitis, priapism, and stroke. Comprehensive care, including family education, immunizations, prophylactic penicillin and prompt treatment of acute illness, reduces morbidity and mortality.

Additional Information:

Grady Comprehensive Sickle Cell Center
<http://scinfo.org/hemoglb.htm#SICKLE%20HEMOGLOBINS>

Management and Therapy of Sickle Cell Disease
<http://www.nhlbi.nih.gov/health/prof/blood/sickle/index.htm>

Sickle Cell Disease in Children and Adolescents: Diagnosis, Guidelines for Comprehensive

Care, and Care Paths and Protocols for Management of Acute and Chronic Complications
<http://www.dshs.state.tx.us/newborn/pdf/sedona02.pdf>

American Academy of Pediatrics
<http://pediatrics.aappublications.org/cgi/content/full/109/3/526>

Sickle Cell Disease Association
<http://www.sicklecelldisease.org/>

Referral (local, state, regional and national): Comprehensive Sickle Cell Center Directory
<http://www.rhofed.com/sickle/index.htm>

Sickle Cell Information Center
<http://www.scinfo.org/clinics.htm>

Increased Methionine

Homocystinuria (CBS Deficiency)

Differential Diagnosis: Classical homocystinuria (cystathionine β -synthase (CBS) deficiency); hypermethioninemia due to MAT I/III deficiency; GAMT deficiency; adenosylhomocysteine hydrolase deficiency; liver disease; hyperalimentation.

Condition Description: Methionine from ingested protein is normally converted to homocysteine. In classical homocystinuria due to CBS deficiency, homocysteine cannot be converted to cystathionine. As a result, the concentration of homocysteine and its precursor, methionine, will become elevated. In MAT I/III deficiency and the other hypermethioninemias, methionine is increased in the absence of, or only with, a slightly increased level of homocysteine.

You Should Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status.
- ◆ Consult with pediatric metabolic specialist. (See attached list.)
- ◆ Evaluate the newborn with attention to liver disease and refer as appropriate.
- ◆ Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.
- ◆ Initial testing: plasma quantitative amino acids, urine organic acids, and plasma total homocysteine.
- ◆ Repeat newborn screen if second screen has not been done.
- ◆ Educate family about homocystinuria and its management as appropriate.
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Quantitative plasma amino acids will show increased homocystine and methionine in classical homocystinuria, but only increased methionine in the other disorders. Plasma homocysteine analysis will show markedly increased homocysteine in classical homocystinuria and normal or only slightly increased homocysteine in the other disorders. Urine homocysteine is markedly increased in classical homocystinuria.

Clinical Considerations: Homocystinuria is usually asymptomatic in the neonate. If untreated, these children eventually develop mental retardation, ectopia lentis, a marfanoid appearance, including arachnodactyly, osteoporosis, other skeletal deformities, and thromboembolism. MAT I/III deficiency may be benign. Adenosylhomocysteine hydrolase deficiency has been associated with developmental delay and hypotonia, and both this disorder and GAMT deficiency can cause liver abnormalities.

Additional Information:

New England Metabolic Consortium – Emergency Protocols

http://www.childrenshospital.org/newenglandconsortium/NBS/met/met_protocol.htm

Gene Tests/Gene Clinics

<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888892&key=HZlogrH0fsXqA&gry=&fcn=y&fw=stEu&filename=/profiles/homocystinuria/index.html>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=homocystinuria>

<http://www.newbornscreening.info/Pro/aminoacid disorders/CBS.html>

<http://www.newbornscreening.info/Parents/aminoacid disorders/CBS.html>

Primary T4-follow-up TSH test/Low T4 and/or Elevated TSH Congenital Hypothyroidism

Differential Diagnosis: Primary and secondary congenital hypothyroidism (CH), transient CH, thyroxine binding globulin (TBG) deficiency.

Condition Description: Lack of adequate thyroid hormone production.

You Should Take the Following Actions

- ◆ Contact family **IMMEDIATELY** to inform them of the newborn screening test result.
- ◆ Consult pediatric endocrinologist; refer to endocrinologist if considered appropriate. (See attached list.)
- ◆ Evaluate infant (see clinical considerations below).
- ◆ Initiate timely confirmatory/diagnostic testing as recommended by the specialist.
- ◆ Initial testing should include free T4 and TSH.
- ◆ Repeat newborn screen if second screen has not yet been done.
- ◆ Initiate treatment as recommended by consultant as soon as possible.
- ◆ Educate parents/caregivers that hormone replacement prevents mental retardation.
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Diagnostic tests should include serum free T4 and thyroid stimulating hormone (TSH); consultant may also recommend total T4 and T3 resin uptake. Test results include reduced free T4 and elevated TSH in primary hypothyroidism. TSH is reduced or inappropriately normal in secondary (hypopituitary) hypothyroidism. Low total T4 and elevated T3 resin uptake are consistent with TBG deficiency.

Clinical Considerations: Most neonates are asymptomatic, though a few can manifest some clinical features, such as prolonged jaundice, puffy facies, large fontanel, macroglossia, and umbilical hernia. Untreated congenital hypothyroidism results in developmental delay or mental retardation and poor growth.

Additional Information:

New England Newborn Screening Program

<http://www.umassmed.edu/nbs/screenings/disorders/hypothyroidism.cfm>

American Academy of Pediatrics

<http://pediatrics.aappublications.org/cgi/content/abstract/91/6/1203>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=congenitalhypothyroidism>

Elevated C5 Acylcarnitine

Isovaleric Acidemia

Differential Diagnosis: Isovaleric acidemia (IVA,) 2-Methylbutyrylglycinuria (2MBG) (also referred to as short/branched chain acyl-CoA dehydrogenase deficiency or SBCAD deficiency); antibiotic-related (pivalic acid derived) artifact.

Condition Description: IVA and 2MBG result from different defects in the metabolism of the branched chain amino acids, leucine (isovaleryl-CoA dehydrogenase in IVA) and isoleucine (short/branched chain acyl-CoA dehydrogenase in 2MBG). In both conditions specific metabolites accumulate and are potentially toxic.

Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, tachypnea, odor of sweaty feet).
- ◆ Consult with pediatric metabolic specialist. (See attached list.)
- ◆ Evaluate the newborn.
- ◆ If infant is ill, initiate emergency treatment as indicated by metabolic specialist and transport IMMEDIATELY to tertiary center with metabolic specialist.
- ◆ Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- ◆ Initial testing: plasma acylcarnitine profile, urine organic acids, urine acylglycines.
- ◆ Repeat newborn screen if second screen not yet done.
- ◆ Educate family about signs/symptoms and need for urgent treatment of metabolic acidosis (poor feeding, vomiting, lethargy, tachypnea, odor of sweaty feet).
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Plasma acylcarnitine analysis confirms the increased C5. Urine organic acid analysis will show isovalerylglycine in IVA and 2-methylbutyrylglycine in most cases of 2MBG. Urine acylglycine and acylcarnitine analysis may also be informative.

Clinical Considerations: Isovaleric acidemia presents in the neonate with metabolic ketoacidosis, a “sweaty feet” odor, dehydration, hyperammonemia, ketonuria, vomiting, hypoglycemia, and failure to thrive. Milder variants without neonatal illness exist. Long-term prognosis of IVA with appropriate therapy is good. The clinical spectrum of 2MBG is variable. To date, most patients identified by newborn screening with 2MBG are of Hmong descent and remain asymptomatic.

Additional Information:

New England Consortium of Metabolic Programs

http://www.childrenshospital.org/newenglandconsortium/NBS/IVA/IVA_protocol.htm

IVA Emergency Protocol

<http://www.childrenshospital.org/newenglandconsortium/NBS/ISOVAL.html>

Gene Tests

<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=TQVVBlc6UfmSh&gry=&fcn=y&fw=Qvcz&ilename=/profiles/oa-overview/index.html>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=isovalericacidemia>

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<http://www.newbornscreening.info/Parents/organicacid disorders/IVA.html>

Elevated C16-OH +/- C18:1-OH and Other Long Chain Acylcarnitines

Long-chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHAD)

Differential Diagnosis: Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency; Trifunctional protein (TFP) deficiency.

Condition Description: LCHAD and TFP deficiencies are fatty acid oxidation (FAO) disorders. FAO occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) after glycogen stores become depleted and energy production relies increasingly on fat metabolism. Fatty acids and potentially toxic derivatives accumulate in FAO disorders, which are caused by deficiency in one of the enzymes involved in FAO.

You Should Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).
- ◆ Consult with pediatric metabolic specialist. (See attached list.)
- ◆ Evaluate infant (hepatomegaly, cardiac insufficiency; history of sudden unexpected death in a sibling; maternal liver disease during pregnancy; hypoglycemia).
- ◆ If signs are present or infant is ill, initiate emergency treatment in consultation with metabolic specialist.
- ◆ Initial testing: plasma acylcarnitine profile and urine organic acids.
- ◆ Repeat newborn screen if the second screen has not been done.
- ◆ Educate family about signs and symptoms of hypoglycemia and metabolic acidosis.
- ◆ Report findings to newborn screening program.

Confirmation of Diagnosis: Hypoglycemia, elevated liver transaminases, bilirubin, lactate, ammonia, and creatine phosphokinase (CPK) are suggestive of LCHAD and TFP deficiencies. Plasma acylcarnitine and urine organic acid analysis are first-line tests to determine if the appropriate LCHAD/TFP profiles are present. Differentiation between both disorders requires further biochemical and molecular genetic testing in cultured fibroblasts derived from a skin biopsy.

Clinical Considerations: LCHAD and TFP deficiencies typically present acutely and are associated with high mortality unless treated promptly; milder variants exist. Hallmark features include hepatomegaly, cardiomyopathy, lethargy, hypoketotic hypoglycemia, elevated liver transaminases, lactic acidosis, and failure to thrive.

Additional Information:

Emergency Treatment Protocol

<http://www.childrenshospital.org/newenglandconsortium/NBS/LCHADD.html>

STAR-G/HRSA -LCHAD

<http://www.newbornscreening.info/Parents/fattyacid disorders/LCHADD.html>
<http://www.newbornscreening.info/Pro/fattyacid disorders/LCHADD.html>

TFP

<http://www.newbornscreening.info/Parents/fattyacid disorders/TFP.html>

Genetics Home Reference

LCHAD

<http://ghr.nlm.nih.gov/condition=longchain3hydroxyacylcoenzym eadehydrogenasedeficiency>

TFP

<http://ghr.nlm.nih.gov/condition=mitochondrialtrifunctionalprotei ndeficiency>

Elevated C8 with Lesser Elevations of C6 and C10 Acylcarnitine Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)

Differential Diagnosis: Medium-chain acyl-CoA dehydrogenase deficiency (MCAD).

Condition Description: MCAD deficiency is a fatty acid oxidation (FAO) disorder. FAO occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) when energy production relies increasingly on fat metabolism. In an FAO disorder, fatty acids and potentially toxic derivatives accumulate because of a deficiency in one of the mitochondrial FAO enzymes.

Medical Emergency: Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).
- ◆ Consult with pediatric metabolic specialist. (See attached list.)
- ◆ Evaluate the newborn (poor feeding, lethargy, hypotonia, hepatomegaly).
- ◆ If signs are present or infant is ill, initiate emergency treatment with IV glucose. Transport to hospital for further treatment in consultation with metabolic specialist.
- ◆ If infant is normal, initiate timely confirmatory/diagnostic testing, as recommended by specialist.
- ◆ Initial testing: plasma acylcarnitine profile; urine acylglycines; urine organic acids and plasma carnitine levels.
- ◆ Repeat newborn screen if the second screen has not been done.
- ◆ Educate family about need for infant to avoid fasting. Even if mildly ill, immediate treatment with IV glucose is needed.
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Plasma acylcarnitine analysis will show elevated octanoylcarnitine (C8). Urine acylglycines will show elevated hexanoylglycine. Diagnosis is confirmed by mutation analysis of the MCAD gene.

Clinical Considerations: MCAD deficiency is usually asymptomatic in the newborn, although it can present acutely in the neonate with hypoglycemia, metabolic acidosis, hyperammonemia, and hepatomegaly. MCAD deficiency is associated with high mortality unless treated promptly; milder variants exist. Hallmark features include vomiting, lethargy, and hypoketotic hypoglycemia. It is a significant cause of sudden death.

Additional Information:

Emergency Treatment Protocol

<http://www.childrenshospital.org/newenglandconsortium/NBS/MCADD.html>

Gene Tests

<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=NexQvDbtfnPSK&gry=&fcn=y&fw=091z&filename=/profiles/mcad/index.html>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=mediumchainacylcoenzymeadehydrogenasedeficiency>

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<http://www.newbornscreening.info/Pro/fattyacid disorders/MCADD.html>

<http://www.newbornscreening.info/Parents/fattyacid disorders/MCADD.html>

Increased Leucine Maple Syrup (Urine) Disease

Differential Diagnosis: Maple syrup urine disease (MSUD); hydroxyprolinemia.

Condition Description: In MSUD, leucine, isoleucine, and valine (branched chain amino acids) cannot be metabolized further than their α -ketoacid derivatives. The amino acids and organic acids accumulate and produce severe toxicity.

Medical Emergency: Take the Following IMMEDIATE Actions

- ◆ **Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, tachypnea).**
- ◆ **Consult with pediatric metabolic specialist. (See attached list.)**
- ◆ **Evaluate the newborn (poor feeding, lethargy, tachypnea, alternating hypertonia/hypotonia, seizures).**
- ◆ **If any sign is present or infant is ill, transport to hospital for further treatment in consultation with metabolic specialist.**
- ◆ **Initiate timely confirmatory/diagnostic testing and management, as recommended by specialist.**
- ◆ **Initial testing: plasma quantitative amino acids and urine organic acids.**
- ◆ **Repeat newborn screen if second screen has not yet been done.**
- ◆ **Provide the family with basic information about MSUD and dietary management.**
- ◆ **Report findings to newborn screening program.**

Diagnostic Evaluation: In MSUD, plasma amino acid analysis reveals elevations of leucine, isoleucine, alloleucine, and valine (the branched chain amino acids) and urine organic acid analysis reveals abnormal branched-chain hydroxyl- and ketoacids. In expanded screening, leucine/isoleucine and hydroxyproline can not be differentiated, so if the baby has hydroxyprolinemia, confirmatory amino acid analysis will show only increased hydroxyproline.

Clinical Expectations: MSUD presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy, and maple syrup odor to urine and cerumen. If untreated, it will progress to irreversible mental retardation, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. Hydroxyprolinemia is probably benign.

Additional Information:

New England Metabolic Consortium – Emergency Protocols

<http://www.childrenshospital.org/newenglandconsortium/NBS/MSUD.html>
http://www.childrenshospital.org/newenglandconsortium/NBS/MSUD/MSUD_protocol.htm

Gene Tests/Gene Clinics

<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=HWrct-uSq-Lup&gry=&fcn=y&fw=FjdM&filena me=/profiles/msud/index.html>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=maplesyrupurinedisease>

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<http://www.newbornscreening.info/Parents/aminoacid disorders/MSUD.html>
<http://www.newbornscreening.info/Pro/aminoacid disorders/MSUD.html>

Increased Phenylalanine

Phenylketonuria (PKU)

Differential Diagnosis: Phenylketonuria (Classical PKU); non-PKU mild hyperphenylalaninemia; pterin defects; transient hyperphenylalaninemia.

Condition Description: In PKU the phenylalanine from ingested protein cannot be metabolized to tyrosine because of deficient liver phenylalanine hydroxylase (PAH). This causes elevated phenylalanine. Pterin defects result from deficiency of tetrahydrobiopterin (BH₄), the cofactor for PAH and other hydroxylases. This produces not only increased phenylalanine but also neurotransmitter deficiencies.

You Should Take the Following IMMEDIATE Actions

- ◆ Contact family immediately to inform them of the newborn screening result.
- ◆ Consult with pediatric metabolic specialist. (See attached list.)
- ◆ Evaluate the newborn and refer as appropriate.
- ◆ Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.
- ◆ Initial testing: plasma/serum phenylalanine.
- ◆ Repeat newborn screen if second screen has not been done.
- ◆ Provide the family with basic information about PKU and dietary management.
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Plasma amino acid analysis which shows increased phenylalanine without increased tyrosine (increased phenylalanine:tyrosine ratio). Urine pterin analysis and red blood cell DHPR assay will identify pterin defects. Consider PAH mutation testing.

Clinical Considerations: Asymptomatic in the neonate. If untreated, PKU will cause irreversible mental retardation, hyperactivity, autistic-like features, and seizures. Treatment will usually prevent these symptoms. Pterin defects cause early severe neurologic disease (developmental delay/seizures) and require specific therapy.

Additional Information:

Genetics Home Reference

PKU

<http://ghr.nlm.nih.gov/condition=phenylketonuria>

Tetrahydrobiopterin Deficiency

<http://ghr.nlm.nih.gov/condition=tetrahydrobiopterindeficiency>

New England Metabolic Consortium

http://www.childrenshospital.org/newenglandconsortium/NBS/pku_protocol.htm

Gene Tests/Gene Clinics

<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=HWrct-uSq-Lup&gry=&fcn=y&fw=t6xL&filename=/profiles/pku/index.html>

STAR G FELSI

<http://www.newbornscreening.info/Parents/aminoacid disorders/PKU.html> <http://www.newbornscreening.info/Pro/aminoacid disorders/PKU.html>

Elevated C3 Acylcarnitine Propionic Acidemia and Methylmalonic Acidemia

Differential Diagnosis: Propionic acidemia (PROP or PA); Methylmalonic acidemias (MMA), including defects in B12 synthesis and transport; maternal severe B12 deficiency.

Condition Description: PROP is caused by a defect in propionyl-CoA carboxylase, which converts propionyl-CoA to methylmalonyl-CoA; MMA results from a defect in methylmalonyl-CoA mutase, which converts methylmalonyl-CoA to succinyl-CoA, or from lack of the required B12 cofactor for methylmalonyl-CoA mutase (cobalamin A, B, C, D, and F).

Medical Emergency: Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, tachypnea).
- ◆ Consult with pediatric metabolic specialist. (See attached list.)
- ◆ Evaluate the newborn; check urine for ketones.
- ◆ If elevated or infant is ill, initiate emergency treatment as indicated by metabolic specialist and transport immediately to tertiary center with metabolic specialist.
- ◆ Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- ◆ Initial testing: plasma amino acids, plasma acylcarnitine profile, and urine organic acids.
- ◆ Repeat newborn screen if second screen has not been done.
- ◆ Educate family about signs, symptoms and need for urgent treatment of hyperammonemia and metabolic acidosis (poor feeding, vomiting, lethargy, tachypnea).
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Plasma acylcarnitine confirms the increased C3. Blood amino acid analysis may show increased glycine. Urine organic acid analysis will demonstrate increased metabolites characteristic of propionic acidemia or increased methylmalonic acid characteristic of methylmalonic acidemia. Plasma total homocysteine will be elevated in the cobalamin C, D, and F deficiencies. Serum vitamin B12 may be elevated in the cobalamin disorders.

Clinical Considerations: Patients with PROP and severe cases of MMA typically present in the neonate with metabolic ketoacidosis, dehydration, hyperammonemia, ketonuria, vomiting, hypoglycemia, and failure to thrive. Long-term complications are common; early treatment may be lifesaving, and continued treatment may be beneficial.

Additional Information:

Emergency Treatment Protocol

PROP <http://www.childrenshospital.org/newenglandconsortium/NBS/PAA.html>

MMA <http://www.childrenshospital.org/newenglandconsortium/NBS/MA.html>

Gene Tests

PROP <http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=NexQvDbtfnPSK&gry=&fnc=y&fw=SoH9&filename=/profiles/oa-overview/index.html>

MMA <http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=NexQvDbtfnPSK&gry=&fnc=y&fw=Qtlb&filename=/profiles/mma/index.html>

Genetics Home Reference

PROP <http://ghr.nlm.nih.gov/condition=propionicacidemia>

MMA <http://ghr.nlm.nih.gov/condition=methylmalonicacidemia>

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<http://www.newbornscreening.info/Pro/facts.html>
<http://www.newbornscreening.info/Parents/facts.html>

Increased Tyrosine Tyrosinemia

Differential Diagnosis: Tyrosinemia I (hepatorenal); Tyrosinemia II (oculocutaneous); Tyrosinemia III; transient hypertyrosinemia; liver disease.

Condition Description: In the hepatorenal form, tyrosine from ingested protein and phenylalanine metabolism cannot be metabolized by fumarylacetoacetate hydrolase to fumaric acid and acetoacetic acid. The resulting fumarylacetoacetate accumulates and is converted to succinylacetone, the diagnostic metabolite, which is liver toxic, and leads to elevated tyrosine. Tyrosinemias II and III are due to other defects in tyrosine degradation.

You Should Take the Following IMMEDIATE Actions

- ◆ Contact family to inform them of the newborn screening result.
- ◆ Consult with pediatric metabolic specialist. (See attached list.)
- ◆ Evaluate the newborn and refer as appropriate.
- ◆ Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.
- ◆ Initial testing: plasma quantitative amino acids; urine organic acids with succinylacetone; and liver function tests.
- ◆ Repeat newborn screen if the second screen has not been done.
- ◆ Provide family with basic information about tyrosinemia.
- ◆ Report findings to newborn screening program.

Diagnostic Evaluation: Plasma amino acid analysis will show increased tyrosine in all of the tyrosinemias. Urine organic acid analysis will reveal increased succinylacetone in Tyrosinemia I.

Clinical Considerations: Tyrosinemia I is usually asymptomatic in the neonate. If untreated, it will cause liver disease and cirrhosis early in infancy. Nitisone (NTBC) treatment will usually prevent these features. Tyrosinemia II is asymptomatic in the neonate, but will cause hyperkeratosis of the skin, corneal ulcers, and in some cases, mental retardation unless treated with a tyrosine restricted diet. Tyrosinemia III may be benign.

Additional Information:

New England Metabolic Consortium

<http://www.childrenshospital.org/newenglandconsortium/NBS/descriptions/tyro1.html>
<http://www.childrenshospital.org/newenglandconsortium/NBS/descriptions/tyro2.html>
<http://www.childrenshospital.org/newenglandconsortium/NBS/descriptions/tyro3.html>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=tyrosinemia>

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<http://www.newbornscreening.info/Parents/aminoacid disorders/Tyrosinemia.html>
<http://www.newbornscreening.info/Pro/aminoacid disorders/Tyrosinemia.html>

Elevated C14:1 +/- Other Long-chain Acylcarnitines

Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)

Differential Diagnosis: Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency.

Condition Description: VLCAD deficiency is a fatty acid oxidation (FAO) disorder. FAO occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) when energy production relies increasingly on fat metabolism. In an FAO disorder, fatty acids and potentially toxic derivatives accumulate because of a deficiency in one of the mitochondrial FAO enzymes.

Medical Emergency: Take the Following IMMEDIATE Actions

- ◆ **Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).**
- ◆ **Consult with pediatric metabolic specialist. (See attached list.)**
- ◆ **Evaluate the newborn (poor feeding, lethargy, hypotonia, hepatomegaly, arrhythmia, evidence of cardiac decompensation).**
- ◆ **If signs are present or infant is ill, initiate emergency treatment with IV glucose and oxygen. Transport to hospital for further treatment in consultation with metabolic specialist.**
- ◆ **If infant is normal, initiate timely confirmatory/diagnostic testing, as recommended by specialist.**
- ◆ **Initial testing: plasma acylcarnitine profile and urine organic acids.**
- ◆ **Repeat newborn screen if second screen has not been done.**
- ◆ **Educate family about need for infant to avoid fasting. Even if mildly ill, immediate treatment with IV glucose is needed.**
- ◆ **Report findings to newborn screening program.**

Diagnostic Evaluation: Plasma acylcarnitine profile may show increased acylcarnitine (and lesser elevations of other long-chain acylcarnitines). Diagnosis is confirmed in consultation with the metabolic specialist by mutation analysis of the VLCAD gene and additional biochemical genetic tests.

Clinical Considerations: VLCAD deficiency may present acutely in the neonate and is associated with high mortality unless treated promptly; milder variants exist. Features of severe VLCAD deficiency include hepatomegaly, cardiomyopathy and arrhythmias, lethargy, hypoketotic hypoglycemia, and failure to thrive. Treatment is available.

Additional Information:

New England Consortium of Metabolic Programs

http://www.childrenshospital.org/newenglandconsortium/NBS/VLCADD/vlcadd_protocol.htm

VLCAD Emergency Protocol

<http://www.childrenshospital.org/newenglandconsortium/NBS/VLCADD.html>

Genetics Home Reference

<http://ghr.nlm.nih.gov/condition=verylongchainacylcoenzymeadehydrogenasedeficiency>

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<http://www.newbornscreening.info/Parents/fattyaciddisorders/VLCADD.html>

<http://www.newbornscreening.info/Pro/fattyaciddisorders/VLCADD.html>