TEXAS Health and Human Services | Texas Department of State Health Services

Newborn Screening ACT Sheet

Elevated C5-OH Acylcarnitine

Organic Acidemias

Differential Diagnosis: 3-methylcrotonyl-CoA carboxylase (3MCC) deficiency (infant or mother); 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. In most of the disorders, the substrate, for which the enzyme is named, and potentially toxic metabolites accumulate.

Conditions associated with this analyte have been identified by the Society of Inherited Metabolic Disorders (SIMD) as critical, and require immediate action.

MEDICAL EMERGENCY - Take the Following IMMEDIATE Actions:

- **Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, and lethargy).**
- **Immediate telephone consultation 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.**
- **Initiate timely confirmatory/diagnostic testing as recommended by specialist.**
- **Initial testing: urine organic acids, urine acylglycine, and plasma acylcarnitine analysis on infant and 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, urine acylglycine, and plasma acylcarnitine on infant and mother. The organic acids analysis on infant and mother should clarify the differential except for holocarboxylase synthetase deficiency. **Biotinidase assay is performed on all newborn screens.**

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 specific to each condition.

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Organic Acidemias

Additional Information:

American College of Medical Genetics and Genomics
https://www.acmg.net/StaticContent/ACT/C5-OH.pdf

Genetics Home Reference
3MCC
http://ghr.nlm.nih.gov/condition/3-methylcrotonyl-coa-carboxylase-deficiency

Beta Ketothiolase deficiency
http://ghr.nlm.nih.gov/condition/beta-ketothiolase-deficiency

HMG CoA lyase deficiency
http://ghr.nlm.nih.gov/condition/3-hydroxy-3-methylglutaryl-coa-lyase-deficiency

3MGA
http://ghr.nlm.nih.gov/condition/barth-syndrome

STAR G FELSI
http://www.newbornscreening.info/Pro/organicaciddisorders/BKD.html
http://www.newbornscreening.info/Pro/organicaciddisorders/HMGCoA.html
http://www.newbornscreening.info/Pro/organicaciddisorders/3MCC.html

TEXAS Health and Human Services | Texas Department of State Health Services

Newborn Screening FACT Sheet

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency (HMG)

What is HMG?

3-hydroxy-3-methylglutaric aciduria (HMG) is a condition in which the body is unable to break down certain proteins. People with the condition are also unable to produce ketone bodies, substances that help the body store energy. HMG is considered an organic acid condition because it can lead to a harmful amount of organic acids and toxins in the body.

Early detection and treatment can often prevent the serious outcomes of this condition.

What Causes HMG?

Enzymes help start chemical reactions in the body. HMG happens when an enzyme called "HMG CoA lyase" is either missing or not working well. This enzyme has two jobs. The first is to help break down leucine. All foods with protein contain leucine. The second job is to help the body make something called "ketone bodies" from stored fat.

What Symptoms or Problems Occur with HMG?

[Symptoms are something out of the ordinary that a parent notices.]

HMG causes periods of illness called Metabolic Crises. Some of the first symptoms are:

- poor appetite
- sleeping longer or more often
- irritable mood/behavior changes (such as crying for no reason)
- muscle weakness

Other problems then follow:

- fever
- diarrhea
- vomiting
- hypoglycemia (low blood sugar)
- increased levels of acid matter in the blood, called metabolic acidosis
- high levels of ammonia in the blood
- enlarged liver

If a Metabolic Crisis is not treated, a child with HMG can develop:

- breathing problems
- seizures
- coma, sometimes leading to death

When not treated, many babies die during their first Metabolic Crisis. Babies who live may have repeated Metabolic Crises that can cause brain damage.

This can result in life-long learning problems or intellectual disabilities and a seizure disorder.

Other problems can include:

- heart enlargement
- pancreatitis (inflamed pancreas gland)
- hearing loss
- vision problems

What is the Treatment for HMG?

The following treatments are often used for babies and children with HMG:

1. Do not go a long time without food – Babies and young children need to eat often to avoid a Metabolic Crisis. Most babies should not go without food for more than 4 to 6 hours. Some babies may need to eat more often. It is important to feed babies during the night. They may need to be woken to eat if they don't wake up on their own.

2. Low-leucine diet, including medical foods and formula – A food plan low in leucine that limits fat and protein is often part of the treatment. High-protein and high-fat foods that your child may need to limit or not eat at all include:

- milk and milk products
- meat, poultry and fish
- eggs
- dried beans and peas
- nuts and peanut butter
- butter, margarine, oil, lard, and foods made with these fats

3. Medications – Taking L-carnitine may help some children. This is safe and natural and helps the body make energy. Use only the form prescribed by your doctor.

Things to Remember

Even minor illnesses such as a cold or the flu can cause a Metabolic Crisis. Call your doctor right away when your child has any of the symptoms or problems mentioned above.

Children who are sick often don't want to eat. If they can't eat, or if they show signs of a Metabolic Crisis, they may need to be treated in the hospital.

3-Methylcrotonyl CoA Carboxylase Deficiency (3MCC)

What is 3MCC?

3-methylcrotonyl-CoA carboxylase deficiency (3-MCC) is a condition in which the body is unable to break down certain proteins properly. 3MCC is considered an organic acid condition because it can lead to harmful amounts of organic acids and toxins in the body. The symptoms of 3MCC vary. Early detection and treatment can often help children with 3MCC lead healthy lives.

What Causes 3MCC?

Enzymes help start chemical reactions in the body. 3MCC happens when an enzyme called "3-methylcrotonyl CoA carboxylase" is missing or doesn't work right. This enzyme helps break down leucine. All foods with protein contain leucine. Harmful matter can build up in the blood and cause problems when someone with 3MCC eats protein.

What Symptoms or Problems Occur with 3MCC?

[Symptoms are something out of the ordinary that a parent notices.]

Symptoms of 3MCC vary. Many people with 3MCC have no symptoms. Others have periods of illness called Metabolic Crises. Some of the first signs are:

- poor appetite
- sleeping longer or more often
- muscle weakness
- irritable mood
- other behavior changes (such as crying for no reason)
- vomiting

If a Metabolic Crisis is not treated, a child with 3MCC might develop:

- breathing problems
- seizures
- liver failure
- coma, sometimes leading to death

Later problems can include:

- low muscle tone
- weakness
- lack of energy
- poor growth

What is the Treatment for 3MCC?

These treatments are sometimes used for babies and children with 3MCC:

1. Low-leucine diet - Most foods in a low-leucine diet will be carbohydrates (such as bread, cereal, noodles, fruits, vegetables). High protein foods to limit or avoid include:

- milk and milk products
- meat and poultry
- fish
- eggs
- dried beans and peas
- nuts/peanut butter

2. Medical foods and formula – There are special medical foods available for people with 3MCC. These foods include special low-protein flours, noodles, and rice. Some children also need a special leucine-free formula. A dietitian will tell you how to use these foods and formula. Dietitians know the right foods for your child to eat.

3. Medications – The doctor may prescribe L-carnitine for your child. This is safe and natural and helps cells make energy. It also helps the body get rid of harmful wastes.

Things to Remember

Minor illnesses such as a cold or flu can cause a Metabolic Crisis in some children with 3MCC. You may need to call your doctor right away when your child has any of the following:

- loss of appetite
- vomiting
- infection or other illness
- fever
- diarrhea

Some children with 3MCC need to eat more starchy foods (such as bread, cereal, and rice) and drink more fluids when they are sick - even if they are not hungry - to avoid a Metabolic Crisis.

Beta Ketothiolase Deficiency
(BKT/BKD)

What is BKT?
Beta-ketothiolase deficiency (BKT) is a condition in which the body is unable to break down certain proteins. People with the condition are also unable to produce ketone bodies, substances that help the body store energy. BKT is considered an organic acid condition because it can lead to a dangerous amount of organic acids and toxins in the body. Early detection and treatment can often prevent the severe outcomes of this condition.

What Causes BKT?
Enzymes help start chemical reactions in the body. BKT happens when an enzyme called "mitochondrial acetoacetyl-CoA thiolase" is missing or not working. This enzyme helps break down the amino acid isoleucine. All foods with protein contain isoleucine. Harmful matter can build up in the blood and cause problems when someone with BKT eats protein.

What Symptoms or Problems Occur with BKT?
[Symptoms are something out of the ordinary that a parent notices.]

BKT can cause periods of illness called Metabolic Crises. Some of the first symptoms of a Metabolic Crisis are:

- too much sleepiness or lack of energy
- fever / vomiting / diarrhea
- poor appetite
- ketones in the urine

Later problems can include:

- intellectual disabilities
- dystonia (muscle spasms)
- enlarged heart
- low blood platelets
- higher risk for infections
- not growing well
- kidney problems

What is the Treatment for BKT?
The treatments often recommended for babies and children with BKT are:

1. Medication – The doctor may prescribe L-carnitine for your child. This is safe and natural and helps the body make energy. It also helps the body get rid of harmful wastes.

2. Do not go a long time without food – Some babies and young children can have a Metabolic Crisis if they don't eat often enough. Your doctor will tell you how to space your child's meals. Most healthy children over the age of 10 can go without food for up to 12 hours without problems.

3. Low-protein diet – Some children will need to eat a low-protein diet. High-protein foods to be limited include:

- milk and milk products
- meat and poultry
- fish
- eggs
- dried beans
- nuts/peanut butter

Children with BKT need some protein to grow properly. A dietitian can make a food plan for your child. Dietitians know the right foods for your child to eat.

Things to Remember
Even minor illness such as a cold or flu can lead to a Metabolic Crisis. Call your doctor right away when your child has any of the following:

- loss of appetite
- vomiting
- diarrhea
- infection or illness
- fever

An ill child with BKT needs more liquids, starchy foods (such as rice, cereal, bread), and sugars to avoid a Metabolic Crisis. When your child is ill, you will also need to limit protein.

Children with symptoms of a Metabolic Crisis need to be treated in a hospital.

TEXAS Health and Human Services | Texas Department of State Health Services

Newborn Screening FACT Sheet

Multiple Carboxylase Deficiency
(Biotinidase and Holocarboxylase Synthase) (MCD)

What is MCD?
Multiple carboxylase deficiency (MCD) is an organic acid disorder. People with MCD can't change protein and carbohydrates from the food they eat into energy for the body.

What Causes MCD?
Enzymes help start chemical reactions in the body. The enzyme holocarboxylase synthetase (HCS) adds the vitamin, biotin, to other enzymes called "carboxylases." These change the food we eat into energy. Harmful matter builds up in the blood and urine when the HCS enzyme doesn't work. This can cause serious health problems.

What Symptoms or Problems Occur with MCD?
[Symptoms are something out of the ordinary that a parent notices.]

MCD causes periods of illness called Metabolic Crises. Some of the first symptoms are:

- poor appetite
- vomiting
- too much sleepiness or lack of energy
- irritable behavior
- low muscle tone (floppy muscles and joints)

If a Metabolic Crisis is not treated, a child with MCD can develop:

- breathing problems
- seizures
- brain swelling
- coma, sometimes leading to death

Later problems can include:

- intellectual disability
- skin rash and hair loss
- unsteady movements
- rigid movement
- vision and hearing loss

What is the Treatment for MCD?
Biotin is usually the only treatment for MCD. Your doctor will prescribe the right amount. This will prevent symptoms in your child. It may rid your child of health problems when symptoms already exist. Early treatment may prevent intellectual disability and other serious medical problems. Treatment should start as soon as you know your child has MCD. Your child will need to take biotin for life.

Things to Remember
Babies who get treatment before they have a Metabolic Crisis usually have normal growth and development.

A few children develop learning problems even when treated. Children may also develop intellectual disability. If treated late, biotin may not reverse all existing symptoms.

TEXAS Health and Human Services | Texas Department of State Health Services

Newborn Screening FACT Sheet

2-Methyl-3-hydroxybutyric acidemia (2M3HBA)

What is 2M3HBA?

2-Methyl-3-hydroxybutyric academia (2M3HBA) is a condition in which the body is unable to break down certain proteins. This condition may also affect the body's ability to break down certain fatty acids and to regulate some activities of the nervous system. 2M3HBA is considered an organic acid condition because it can lead to a harmful amount of certain organic acids and toxins in the body. Early diagnosis and treatment have been shown to be effective in improving the health of individuals affected by 2M3HBA.

What Causes 2M3HBA?

When we eat, enzymes help break the food down. Some enzymes break down proteins into their building blocks, amino acids. Other enzymes break down these amino acids. In the disorder, 2M3HBA, the enzyme 2-methyl-3-hydroxybutyrl is not working correctly. This enzyme's job is to break down the amino acid isoleucine and some fats called branched-chain fatty acids. This enzyme is also involved with hormones. Hormones regulate the body's activities, such as sexual development and nerve signals.

If your baby has 2M3HBA, his or her body is missing or making non-working 2-methyl-3-hydroxybutyrl-CoA dehydrogenase enzymes. When this enzyme is not working correctly, your baby's body cannot break down isoleucine, which causes harmful substances to build up in your baby's body. This can be toxic.

What Symptoms or Problems Occur with 2M3HBA?

[Symptoms are something out of the ordinary that a parent notices.]

Children with 2M3HBA start showing signs during infancy, typically between 9 and 14 months. Males and females can have different signs of 2M3HBA.

Males are more severely affected than females. Males might experience:

- difficulty with movements of their muscles
- loss of the developmental milestones met prior to age 5 (also known as regression)
- loss of motor skills.

Females are less severely affected by 2M3HBA. Females affected by this condition may experience:

- mild developmental delays (but no regression)

Both males and females may experience:

- sleeping longer or more often
- tiredness
- loss of appetite
- weak muscle tone (also called hypotonia)
- epilepsy (seizures)

Many of these signs occur when your baby eats foods that his or her body cannot break down. They can be triggered by long periods of time without eating, illnesses, and infections.

If your baby shows any of these signs, contact your baby's doctor immediately.

What is the Treatment for 2M3HBA?

Your baby will need a carefully planned diet to avoid the proteins that your baby's body cannot break down. When your baby eats fats and proteins that he or she cannot break down, it may cause many of the signs mentioned in the "Symptoms or Problems" section. A metabolic doctor or a dietician can help you plan a well-balanced diet for your child.

Your baby will also need to eat often because long periods of time without food can trigger many of the signs mentioned in the Signs and symptoms section. Illness and infections can also trigger these signs.

Things to Remember:

Restricted diets have been effective for children who have been treated for 2M3HBA, but we do not know what kinds of long-term effects this treatment could have.

Children with 2M3HBA may develop intellectual disabilities, even if they receive treatment. Males are at risk for severe intellectual disabilities, and females are at risk for mild intellectual disabilities.

TEXAS Health and Human Services | Texas Department of State Health Services

Newborn Screening FACT Sheet

3-Methylglutaconic Aciduria
(3MGA)

What is 3MGA?
3-methylglutaconic aciduria (3MGA) is the name for a group of five different conditions. All of these conditions affect the body's mitochondria, the part of a human cell that produces energy. The causes, symptoms, and treatment of the five different types of 3MGA vary. However, all types of 3MGA are classified as organic acid conditions because they can result in a build-up of harmful amounts of organic acids and toxins in the body.

What Causes 3MGA?
When we eat food, enzymes help break it down. Some enzymes help break down proteins into their building blocks, called amino acids. Other enzymes break down the amino acids.

TYPE I
The enzyme 3-methylglutaconyl-CoA hydratase is an enzyme that helps break down the amino acid leucine. When your baby has 3MGA type I, his or her body does not make enough or makes non-working 3-methylglutaconyl-CoA hydratase. When this happens, your baby's body cannot break down leucine. This causes a build-up of harmful substances in the body.

Type II (Barth Syndrome)
When your baby has 3MGA type II, his or her body is not making enough of a protein called tafazzin. Tafazzin helps balance the levels of a type of fat called cardiolipin in cells. Cardiolipin helps cells make energy. When your baby's body does not have tafazzin, the cells have trouble making energy.

Type III
When your baby has 3MGA type III, his or her body does not make enough of a protein known as the OPA3 protein. We do not yet know what the role of this protein is in the body.

Type IV
Currently, we do not understand what causes 3MGA type IV.

Type V
When your baby has 3MGA type V, his or her body does not make enough of a protein known as the DNAJC19 protein. Currently, we do not know what this protein does, but some researchers think that it might help make, move, and break down other proteins in the cells.

All types of 3MGA are genetic conditions, but they are not all passed down in the same way. Types I, III, and V are autosomal recessive genetic conditions. This means that a child must inherit one copy from each parent of the non-working gene for that type of 3MGA in order to have the condition. The parents of a child with an autosomal recessive condition each carry one copy of the non-working gene, but they typically do not show signs and symptoms of the condition. While having a child with 3MGA is rare, when both parents are carriers, they can have more than one child with the condition. Learn more about autosomal recessive inheritance at **www.babysfirsttest.org/genetics.**

Type II is an X-linked recessive genetic condition. This means that a male must inherit one copy of the non-working gene from his mother to have the condition. A female must inherit two copies of the non-working gene, one from each parent, in order to have the condition. In X-linked conditions, the gene is carried on the X sex chromosome, and the condition affects males more than females. While having a child with 3MGA is rare, when one or both parents carry the non-working gene for 3MGA type II, they can have more than one child with the condition. Learn more about X-linked recessive inheritance at **www.babysfirsttest.org/genetics.**

3-Methylglutaconic Aciduria
(3MGA)

What Symptoms or Problems Occur with 3MGA?
[Symptoms are something out of the ordinary that a parent notices.]

The signs of 3-methylglutaconic aciduria (3MGA) differ depending on type, but they all begin in utero or at birth.

3MGA type I signs include:
- delays in reaching developmental milestones (such as speech or motor skills)
- irregular, uncontrolled muscle movements (called dystonia)
- muscle spasms and weakness in the arms and legs (called spastic quadriparesis)

3MGA type II (Barth syndrome) signs include:
- frequent infections
- weak muscles
- delayed growth
- heart problems

3MGA type III (Costeff optic atrophy syndrome) signs include:
- vision loss
- trouble with balance
- weak muscle tone (called hypotonia)
- involuntary and irregular movements

3MGA type IV signs vary from individual to individual. Type IV has signs similar to types I, II, and III.

3MGA type V (dilated cardiomyopathy with ataxia) signs include:
- difficulty coordinating voluntary muscle movements (called ataxia)
- delayed growth
- undescended testes or an opening in the urethra on the underside of the penis

What is the Treatment for 3MGA?
The best way to care for your baby is to monitor your baby's heart for any cardiac complications by regularly visiting a cardiologist and metabolic specialist. A cardiologist can identify changes in your baby's heart and decide if any additional treatments are necessary. Each baby with 3MGA experiences unique signs and symptoms, so it is important to talk to your baby's doctor to decide which treatment is right for your baby.

Other than following up with a cardiologist as necessary, there are no specific treatments available for 3MGA.

Things to Remember
Work with your baby's doctor to determine the next steps for your baby's care. Your child's health care provider will help you coordinate care with other medical resources in the community. Care depends on what type of 3MGA your child has and on your child's symptoms.

Some children will need specialized care from a cardiologist, a metabolic specialist, a dietician, and/or an optometrist. Some children with 3MGA have developmental delays.

If you think that your baby is not meeting his or her developmental milestones, ask your child's health care provider about the next steps in accessing a developmental evaluation and care.