

Newborn Screening ACT Sheet

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: Propionic acidemia (PA); 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 (MUT), which converts methylmalonyl-CoA to succinyl-CoA, or from lack of the required B12 cofactor for methylmalonyl-CoA mutase (cobalamin A, B, C, D, E, F, G, and J).

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 Action

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, and tachypnea).
- Immediate telephone consultation with pediatric metabolic specialist (See attached list).
- Evaluate the newborn; check urine for ketones, and 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 labs: plasma acylcarnitine profile, plasma total homocysteine, plasma methylmalonic acid, 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, E, F, G and J deficiencies. Serum vitamin B12 may be elevated in the cobalamin disorders.

Clinical Considerations: Patients with PA 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:

American College of Medical Genetics and Genomics

<https://www.acmg.net/StaticContent/ACT/C3.pdf>

Genetics Home Reference

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

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

STAR G FELSI

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

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

Newborn Screening FACT Sheet

Propionic Acidemia (PROP or PA)

What is PROP?

Propionic acidemia (PROP) is an inherited condition in which the body is unable to break down certain proteins and fats. It is considered an organic acid condition because it can lead to a harmful amount of organic acids and toxins in the body. If left untreated, it can cause brain defects or even death. However, if the condition is identified early in life and proper treatment is begun, children with PROP can minimize some of the early complications of the condition.

What Causes PROP?

Enzymes help start chemical reactions in the body. PROP happens when an enzyme called “propionyl CoA carboxylase” (PCC) is missing or not working. This enzyme changes certain amino acids so the body can use them. Glycine and propionic acid build up in the blood and cause problems when PCC doesn’t work.

What Symptoms or Problems Occur with PROP?

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

PROP causes periods of illness called Metabolic Crises. Early symptoms of a Metabolic Crisis are:

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

If a Metabolic Crisis isn’t treated, a child with PROP can develop:

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

Later problems can include:

- intellectual disabilities
- low ability to fight illnesses
- osteoporosis (weak bones)
- inflamed pancreas gland
- skin rashes
- poor growth

What is the Treatment for PROP?

The following treatments are often used for children with PROP:

1. Low-protein diet, medical foods and medical formula – The best treatment for PROP is a diet low in protein. Most of the low-protein food will be carbohydrates (such as bread, cereal, noodles, fruits, vegetables). High-protein foods that should be limited or not eaten at all include:

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

The doctor may prescribe a special medical formula with the right amount of protein. There are also medical foods available for people with PROP.

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. They shouldn’t go without food for more than 4 to 6 hours. Some children may need to eat even more often. Your dietitian can give ideas for suitable snacks and knows the right foods for your child to eat.

3. Medication – The doctor may prescribe L-carnitine for your child. This is safe and natural and helps the body make energy.

Things to Remember

Even minor illness such as a cold or flu can cause 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

Many children with PROP must be treated in the hospital during illness to avoid serious health problems.



Newborn Screening FACT Sheet

Methylmalonic Acidemia (MMA)

What is MMA?

Methylmalonic acidemia (MMA) is a condition with many different forms, all of which have different causes and treatments. Methylmalonic acidemia caused by methylmalonyl-CoA mutase deficiency is just one type of MMA. In addition methylmalonic acidemia can be caused by cobalamin disorders A and B, or methylmalonic acidemia with homocystinuria, which is caused by cobalamin disorders C, D, E, F, G and J.

What Causes MMA?

Enzymes help start chemical reactions in the body. Special enzymes break down certain amino acids and fatty acids from the protein in food so that the body can use them. MMA happens when one of these special enzymes is missing or not working. There are a number of different kinds of MMA. Some improve with Vitamin B12 injections (Vitamin B12-responsive), and some do not (Vitamin B12 non-responsive).

What Symptoms or Problems Occur with MMA?

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

MMA causes periods of illness called Metabolic Crises. Some of the first symptoms of a Metabolic Crisis are:

- poor appetite
- low muscle tone (floppy arms and legs)
- vomiting
- too much sleepiness or lack of energy

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

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

Later problems can include:

- intellectual disabilities
- low ability to fight illnesses
- poor growth
- muscle spasms
- kidney problems
- skin rashes
- tight muscles
- brittle bones

What is the Treatment for MMA?

1. Medication – Vitamin B12 shots are the main treatment for Vitamin B12 -responsive MMA, caused by not enough cobalamin A & B. Vitamin B12 helps most children with the first form (A). It helps close to half of children with the second form (B). Your child's doctor may prescribe L-carnitine. This is safe and natural and helps body cells make energy. Antibiotics may help.

2. Low-protein diet, medical foods and medical formula – Foods high in protein should be limited or not eaten at all. They include:

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

The doctor may give your child a special medical formula. A dietitian will tell you what kind of formula is best and how much to use. A nutritionist or dietician can help you plan a healthy diet for your child.

Things to Remember

Even minor illness can lead to a Metabolic Crisis in children with MMA. Call your doctor right away when your child has any of the following:

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

Children need extra fluids and starchy food (such as bread, rice, cereal, noodles) when they're sick in order to prevent a Metabolic Crisis. During illness, you should limit protein and give your child starchy foods and fluids. Sick children with MMA may need to be treated in the hospital to avoid serious health problems.

Newborn Screening FACT Sheet

Methylmalonic Acidemia (MMA) Cobalamin A, B Type (Cbl A, B)

What is Methylmalonic Acidemia Cobalamin A, B Type (Cbl A, B)?

Methylmalonic acidemia (MMA) is a condition with many different forms, which all have different causes and treatments. Methylmalonic acidemia caused by cobalamin disorders A and B (Cbl A, B) is just one type of MMA.

MMA is a condition in which the body is unable to break down certain fats and proteins. It is considered an organic acid condition because it can lead to a harmful amount of organic acids and toxins in the body. MMA caused by cobalamin A or cobalamin B deficiencies is one type of MMA. Children with this form of the condition have trouble producing cobalamin enzymes A and B. Cobalamin enzymes are necessary for the body to break down certain foods.

What Causes MMA Cbl A, B?

When we eat food, enzymes help to break it down. Some enzymes break down proteins into their building blocks, amino acids. Other enzymes break down these amino acids. In Cbl A, B, the enzymes “cobalamin A” and “cobalamin B” are not working correctly. Cbl A, B enzymes help break down amino acids. Children with Cbl A, B either do not make enough or make non-working Cbl A, B enzymes. When these enzymes do not work, their bodies cannot break down the amino acids isoleucine, valine, methionine, and threonine. This causes a build-up of harmful substances in the body.

Cbl A, B is an autosomal recessive genetic condition. This means that a child must inherit two copies of the non-working gene for Cbl A, B, one from each parent, 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 Cbl A, B is rare, when both parents are carriers, they can have more than one child with the condition.

What Symptoms or Problems Occur with MMA Cbl A, B Type?

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

Early Signs

The signs of MMA Cbl A, B can begin at any time from birth to adulthood. In most cases, signs first appear during infancy (as early as the first few days after birth). For babies, signs of Cbl A, B can include:

- sleeping longer or more often
- vomiting
- weak muscle tone (also called hypotonia)
- fever
- breathing trouble
- frequent illnesses and infections
- increased bleeding and bruising

Many of these signs may 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, be sure to contact your baby’s doctor immediately.

What is the Treatment for MMA Cbl A, B Type?

Supplements and Medications - There are two types of MMA: cobalamin disorders and MUT deficiencies. One of the ways these two types of MMA differ is their response to vitamin B12. MUT deficiencies are considered non-vitamin B12 responsive.

Cobalamin deficiencies are vitamin B12 responsive. In these cases, vitamin B12 injections can prevent symptoms. This type of treatment is more successful for cobalamin A disorders than for cobalamin B disorders, but it is helpful for both.

Your baby’s doctor might also recommend L-carnitine supplements. These supplements help the body break down fats and they can remove harmful substances from the body. Your baby’s doctor will need to write a prescription for these supplements.

Methylmalonic Acidemia (MMA) Cobalamin A, B Type (Cbl A, B)

Dietary Treatment – Some forms of Cobalamin A and B may not require dietary management. Other children may need a very carefully monitored diet. Children with MMA need to avoid certain fats and proteins because their bodies cannot break down these substances. Your baby's doctor can recommend special formulas made for babies with organic acid conditions. These formulas will likely need to be continued through adulthood.

It is also important for your baby to eat frequently. Long periods without food, illnesses, and infection may trigger many of the signs mentioned in the Early Signs section.

Things to Remember

Even minor illness can lead to a Metabolic Crisis in children with MMA Cbl A, B Type. Call your doctor right away when your child has any of the following:

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

Children need extra fluids and starchy food (such as bread, rice, cereal, noodles) when they're sick in order to prevent a Metabolic Crisis.

During illness, you should limit protein and give your child starchy foods and fluids. Sick children with MMA Cbl A, B may need to be treated in the hospital to avoid serious health problems.

Work with your baby's doctor to determine the next steps for your baby's care. Your baby's doctor will help you coordinate care with a physician who specializes in metabolism, a dietician who can help plan your child's specialized diet, or other medical resources in your community.

Some children with MMA have developmental delays. If you think that your baby is not meeting his or her developmental milestones, ask your baby's doctor about the next steps in requesting a developmental evaluation and care.

Newborn Screening FACT Sheet

Methylmalonic Acidemia (MMA) with Homocystinuria (Cbl C, D, E, F, G, and J)

What is Methylmalonic Acidemia (MMA) with homocystinuria (Cbl C, D, E, F, G, and J)?

MMA is a condition in which the body is unable to process certain fats and proteins. It is considered an organic acid condition because it can lead to a harmful excess of certain toxins and organic acids. MMA with homocystinuria (Cbl C, D, E, F, G, and J) is one type of MMA. Individuals with this form of MMA have trouble producing certain cobalamin enzymes, which causes harmful levels of homocysteine and methylmalonic acid to build up in their bodies.

What Causes Cbl C, D, E, F, G, or J?

When we eat food, enzymes help break it down. Certain enzymes break down proteins into their building blocks, amino acids. Other enzymes break down these amino acids.

Some enzymes need help from vitamins like vitamin B12 (also called cobalamin). The enzymes that break down the amino acids isoleucine, valine, methionine, and threonine need vitamin B12 to work correctly.

If your baby has Cbl C, D, E, F, G, or J, his or her body cannot use vitamin B12 correctly. Your baby's body either does not make enough or makes non-working enzymes that are supposed to turn vitamin B12 from food into a form that the body can use.

Cbl C, D, E, F, G, and J is an autosomal recessive genetic condition. This means that a child must inherit two copies of the non-working gene for Cbl C, D, E, F, G, or J one from each parent, 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 Cbl C, D, E, F, G, or J is rare, when both parents are carriers, they can have more than one child with the condition.

What Symptoms or Problems Occur with Cbl C, D, E, F, G, or J [Symptoms are something out of the ordinary that a parent notices.]

Signs of Cbl C, D, E, F, G, or J could begin anywhere between the first few days of life and 14 years of age. Children with Cbl C usually show symptoms between the first few days and the first month of life.

Children with Cbl D deficiency do not show signs until later in childhood. If your baby has Cbl C, D, E, F, G, or J you might notice signs including:

- delayed growth
- small head size
- skin rash
- vomiting
- poor appetite
- diarrhea
- fever
- sleeping longer or more often
- tiredness
- weak muscle tone (called hypotonia)

Many of these signs may 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, be sure to contact your baby's health care provider immediately.

What is the Treatment for Cbl C, D, E, F, G, or J?

Dietary Treatment - Your baby will probably need to be on a restricted diet to avoid proteins that his or her body cannot break down. A dietician or nutritionist can help you plan a low-protein diet that still gives your baby the right nutrients for healthy growth.

Your baby's doctor might recommend special formulas or foods especially for children with Cbl C, D, E, F, G, or J. These formulas will likely need to continue through adulthood.

Eating often will also help prevent your baby from experiencing many of the signs mentioned in the previous section. Illnesses and infections can also trigger these signs.

Supplements and Medications - Supplements can also help treat Cbl C, D, E, F, G, or J. Vitamin B12 can help reduce the signs and symptoms of the condition in some children. Your baby's doctor may need to try this treatment for a short period of time in order to determine if it is an effective treatment for your baby. Talk to your baby's doctor before starting vitamin B12 treatment.

Newborn Screening FACT Sheet (Page 2)

Methylmalonic Acidemia (MMA) with Homocystinuria (cbl C, D, E, F, G, and J)

L-carnitine is another substance that helps get rid of harmful waste products in the body. Some babies do not need this supplement, but your baby's body might not be making enough carnitine naturally. Your baby's doctor can tell if your baby needs these supplements and write an appropriate prescription.

Betaine supplements can help lower homocysteine levels in your baby's blood. Your baby's doctor can write a prescription for these supplements.

Things to Remember

Even minor illness can lead to a Metabolic Crisis in children with Cbl C, D, E, F, G, or J. Call your doctor right away when your child has any of the following:

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

Children need extra fluids and starchy food (such as bread, rice, cereal, noodles) when they're sick in order to prevent a Metabolic Crisis. During illness, you should limit protein and give your child starchy foods and fluids. Sick children with Cbl C, D, E, F, G, or J may need to be treated in the hospital to avoid serious health problems.

Work with your baby's doctor to determine the next steps for your baby's care. Your baby's doctor may help you coordinate care with a physician who specializes in metabolism, a dietitian who can help plan your child's specialized diet, or other medical resources in your community. Some children Cbl C, D, E, F, G, or J have developmental delays. If you think that your baby is not meeting his or her developmental milestones, ask your baby's doctor about the next steps in requesting a developmental evaluation and care.

Newborn Screening FACT Sheet

Methylmalonic Acidemia Mutase Deficiency (methylmalonyl-CoA mutase deficiency) (MUT)

What is Methylmalonic Acidemia Mutase Deficiency?

Methylmalonic acidemia (MMA) is a condition with many different forms, all of which have different causes and treatments. MMA caused by methylmalonyl-CoA mutase deficiency is just one type of MMA.

What Causes MMA Mutase Deficiency?

When we eat food, enzymes help break it down. Some enzymes break down proteins into their building blocks, amino acids. Other enzymes break down fats into their building blocks, fatty acids. More enzymes break down these amino acids and fatty acids.

In MMA, the enzyme methylmalonyl-CoA mutase is not working correctly. This enzyme helps break down odd-chain fatty acids and the amino acids isoleucine, valine, methionine, and threonine. If your baby is affected with MMA mutase deficiency, then his or her body is either not making enough or making non-working methylmalonyl-CoA mutase enzymes.

In “MMA mutase deficiency 0” forms of MMA mutase deficiency, this enzyme is completely deficient. That means that there are no working methylmalonyl-CoA mutase enzymes in the body. In the “MMA mutase deficiency+” forms, some methylmalonyl-CoA mutase enzymes work correctly, but there are not enough. Without enough working enzymes, your baby’s body has trouble using fats and proteins for energy.

MMA mutase deficiency is an autosomal recessive genetic condition. This means that a child must inherit two copies of the non-working gene for MMA mutase deficiency, one from each parent, 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 MMA mutase deficiency is rare, when both parents are carriers, they can have more than one child with the condition.

What Symptoms or Problems Occur with MMA Mutase Deficiency?

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

Early Signs -Signs of MMA mutase deficiency can start at any time from birth to adulthood. In most cases, the signs begin during infancy (either in the first few days or in the first few months of life). For babies, signs of MMA mutase deficiency can include:

- sleeping longer or more often
- tiredness
- vomiting
- weak muscle tone (also called hypotonia)
- fever
- breathing trouble
- frequent illnesses and infections
- increased bleeding and bruising

Many of these signs may 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, be sure to contact your baby’s doctor immediately.

What is the Treatment for MMA Mutase Deficiency?

There are two types of MMA: cobalamin disorders and MMA mutase deficiency. Cobalamin disorders are considered vitamin B12 responsive. MMA mutase deficiency deficiencies are non-vitamin B12 responsive. You may hear about other babies with MMA receiving vitamin B12 injections. This treatment will not help a baby with MMA mutase deficiency.

Supplements and Medication - Your baby’s doctor might recommend L-carnitine supplements. These supplements help the body break down fats, and they can remove harmful substances from the body. Your baby’s doctor will need to write a prescription for these supplements.



Newborn Screening FACT Sheet (Page 2)

Methylmalonic Acidemia Mutase Deficiency (methylmalonyl-CoA mutase deficiency) (MUT)

Dietary Treatments - Your baby will need a very carefully monitored diet. Children with MMA need to avoid certain fats and proteins because their bodies cannot break down these substances, causing a buildup of toxic substances. Your doctor can recommend special formulas and foods made for children with organic acid conditions. These formulas will likely need to be continued through adulthood.

It is also important for your baby to eat frequently. Long periods of time without food, illness, or infections may trigger many of the signs mentioned in the previous section.

Things to Remember

Even minor illness can lead to a Metabolic Crisis in children with MMA mutase deficiency. Call your doctor right away when your child has any of the following:

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

Children need extra fluids and starchy food (such as bread, rice, cereal, noodles) when they're sick in order to prevent a Metabolic Crisis. During illness, you should limit protein and give your child starchy foods and fluids. Sick children with MMA mutase deficiency may need to be treated in the hospital to avoid serious health problems.

Work with your baby's doctor to determine the next steps for your baby's care. Your baby's doctor may help you coordinate care with a physician who specializes in metabolism, a dietician who can help plan your child's specialized diet, or other medical resources in your community. Some children with methylmalonic acidemia have developmental delays. If you think that your baby is not meeting his or her developmental milestones, ask your baby's health care provider about the next steps in requesting a developmental evaluation and care.