Genetic Fact Sheets for Parents

Organic Acid Disorders

Screening, Technology, and Research in Genetics is a multi-state project to improve information about the financial, ethical, legal, and social issues surrounding expanded newborn screening and genetic testing – http:// www.newbornscreening.info

Disorder name: **Methylmalonic Acidemia with Homocystinuria**
Acronym: There is no standard acronym for this condition.
For this fact sheet we will use **MMA+HCU**

This fact sheet contains general information about methylmalonic acidemia with homocystinuria (MMA+HCU). Every child is different and some of these facts may not apply to your child specifically. Certain treatments may be recommended for some children but not others. All children with MMA+HCU should be followed by a metabolic doctor in addition to their primary care provider.

What is MMA+HCU?

MMA+HCU stands for “methylmalonic acidemia with homocystinuria”. It is one type of **organic acid disorder**. People with MMA+HCU have problems breaking down and using certain amino acids and fatty acids from the food they eat.

Organic Acid Disorders:

Organic acid disorders (OAs) are a group of rare inherited conditions. They are caused by enzymes that do not work properly. A number of enzymes are needed to process protein from the food we eat for use by the body. Problems with one or more of these enzymes can cause an organic acid disorder.

People with organic acid disorders cannot break down protein properly. This causes harmful substances to build up in their blood and urine. These substances can affect health, growth and learning.

The symptoms and treatment vary between different organic acid disorders. They can also vary from person to person with the same organic acid disorder. See the fact sheets for each specific organic acid disorder.

Organic acid disorders are inherited in an autosomal recessive manner and affect both males and females.

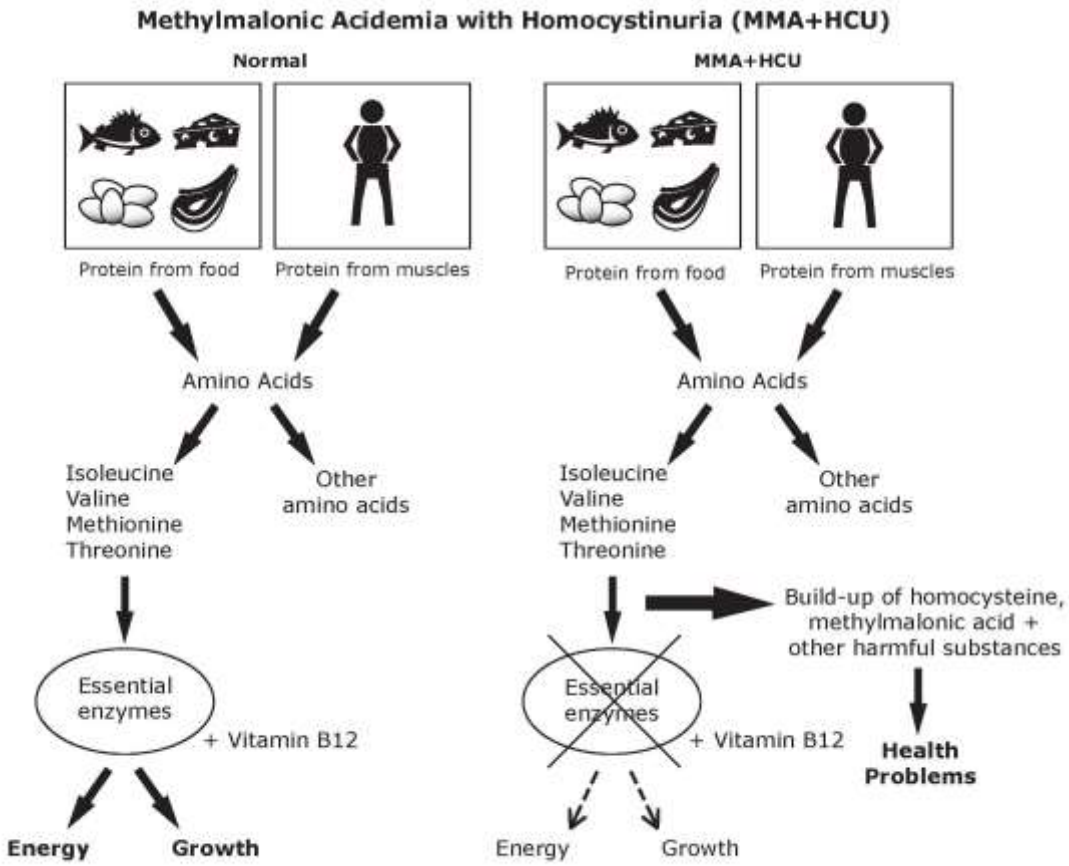
What causes MMA+HCU?

In order for the body to use protein from the food we eat, it is broken down into smaller parts called amino acids. Special enzymes then make changes to the amino acids so the body can use them. In the same way, fat from the food we eat is broken down into fatty acids that the body can use for energy.

MMA+HCU occurs when one of these special enzymes is either missing or not working properly. The job of these enzymes is to change vitamin B12 (also called cobalamin) into a form that the body can use. When the body is not able to use vitamin B12 correctly, it causes homocysteine, methylmalonic acid and other harmful substances to build up in the blood. This can lead to serious health problems.

There are a number of forms of MMA+HCU. The most common form is called Cobalamin C deficiency (CblC). Rarer forms include Cobalamin D deficiency (CblD) and Cobalamin F deficiency (CblF).

There are other forms of MMA that occur without homocystinuria. These are described in a separate fact sheet - see **MMA**.



Isoleucine, valine, methionine, and threonine are the four amino acids that cannot be used correctly by people with MMA+HCU. They are found in all foods that contain protein. Large amounts are found in meat, eggs, milk, and other dairy products. Smaller amounts are found in flour, cereal, and some vegetables and fruits.

If MMA+HCU is not treated, what problems occur?

Each child with MMA+HCU is likely to have somewhat different effects:

- Most babies with CblC deficiency have shown symptoms within the first year, often by one month of age. A small number of children with CblC deficiency have not had symptoms until after 4 years of age. A small number of individuals have been reported to have developed their first symptoms in their teens or early twenties.
- Babies with CblF deficiency usually have their first symptoms shortly after birth.
- Children with CblD deficiency usually show initial symptoms later in childhood.

It is possible that a small number of people with this condition never develop symptoms.

Early-onset MMA+HCU

In babies who have symptoms, common findings are:

- poor appetite
- poor growth
- extreme sleepiness or lack of energy
- low muscle tone (floppy muscles and joints)
- seizures
- small head and brain size, called microcephaly
- water on the brain, called hydrocephalus
- other brain abnormalities
- delays in learning or intellectual disabilities
- vision problems
- heart problems
- kidney problems
- skin rashes

Lab findings can include:

- high levels of homocysteine and methylmalonic acid in the blood and urine
- high levels of acidic substances in the blood, called metabolic acidosis
- protein or blood in the urine
- anemia
- low platelets
- low white blood cells
- excess clotting of the blood

If not treated, metabolic acidosis can cause:

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

Metabolic acidosis and other symptoms can be triggered by:

- eating large amounts of protein
- illness or infection
- going too long without food
- stressful events such as surgery

Later-onset MMA+HCU

Children who do not have symptoms until later in childhood often have some or all of the following symptoms:

- sudden loss of mental skills
- forgetfulness and confusion
- episodes of psychosis or delirium
- behavior problems
- tremor
- numbness or weakness in the limbs
- unsteady gait
- slurred speech
- blood clots
- anemia, low platelets, and/or low white blood cells
- vision problems
- kidney problems

What is the treatment for MMA+HCU?

Your baby's primary doctor will work with a metabolic doctor and a dietician familiar with MMA+HCU to care for your child.

It is not known how effective treatment is in preventing effects of MMA+HCU. However, prompt and ongoing treatment may lessen the chance for intellectual disabilities, psychiatric disorders, and serious health problems.

Most children need to be on a low-protein diet and drink a special medical formula. Many children are given injections of vitamin B12. It is important to start treatment as soon as you know your child has MMA+HCU.

The following are treatments often recommended for children with MMA+HCU:

1. Low-protein diet, medical foods and medical formula

Low-protein diet

A food plan low in the amino acids leucine, valine, methionine, and threonine with limited amounts of protein is often recommended. Most food in the diet will be carbohydrates (bread, cereal, pasta, fruit, vegetables, etc.). Carbohydrates give the body many types of sugar that can be used as energy. Eating a diet high in carbohydrates and low in protein and fat can help prevent metabolic crises.

Foods high in protein that may need to be avoided or limited include:

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

Many vegetables and fruits have only small amounts of protein and can be eaten in carefully measured amounts. Do not remove all protein from the diet. Children with MMA+HCU need a certain amount to grow properly.

Your dietician can create a food plan that contains the right amount of protein, nutrients, and energy to keep your child healthy. Your child will need to be on a special food plan throughout life.

Medical formula and foods

In addition to a low-protein diet, your child may be given a special formula. This formula contains the correct amount of protein and nutrients needed for normal growth and development. Your metabolic doctor and dietician will tell you whether your child needs formula, what type is best, and how much to use.

There are also medical foods such as special low-protein flours, pastas, and rice that are made especially for people with organic acid disorders. Your dietician will tell you how to use these foods as part of your child's diet.

Some states offer help with payment or require private insurance to pay for the formula and other special medical foods.

2. Medication

Vitamin B12

Babies and children with MMA+HCU may be given vitamin B12 injections in the form of hydroxocobalamin (OH-cbl). This treatment seems to lessen the symptoms in some children but not others. Your doctor may need to treat your child with OH-cbl for a short period of time to determine whether this treatment is useful.

L-Carnitine

Some children with MMA+HCU may benefit by taking L-carnitine. This is a safe and natural substance that helps the body make energy. It also helps get rid of harmful wastes. Your doctor will decide whether or not your child needs L-carnitine. Unless you are advised otherwise, use only L-carnitine prescribed by your doctor.

Betaine

Betaine is a vitamin-like substance found in grains and other foods. It can also be bought in pill form as a supplement. Betaine helps lower the amount of homocysteine in the blood. It may lessen the risk of blood clots. Your metabolic specialist will decide whether your child needs betaine. He or she will need to write a prescription.

Hospital care

Children with extreme sleepiness or lack of energy and those who are ill may need to be treated in the hospital. If your child has metabolic acidosis, he or she may be given medications such as bicarbonate by IV to help reduce the acid levels in the blood. Glucose is given by IV to prevent the breakdown of body stores of protein and fat.

Do not use any medication without checking with your doctor or metabolic specialist.

3. Avoid going a long time without food

Infants and young children with MMA+HCU need to eat frequently to prevent a metabolic crisis. Your metabolic doctor will tell you how often your child needs to be fed. In general, it is often suggested that infants be fed every four to six hours. Some babies need to eat even more frequently than this. It is important that infants be fed during the night. They may need to be woken up to eat if they do not wake up on their own. Your metabolic doctor and dietician will give you an appropriate feeding plan for your infant. Your doctor will also give you a 'sick day' plan, tailored to your child's needs, for you to follow during illnesses or other times when your child will not eat.

Your metabolic doctor will continue to advise you on how often your child should eat as he or she gets older.

4. Regular blood and urine tests

Your child will likely need regular blood and urine tests to measure the level of amino acids and other substances. Your child's diet and medication may need to be adjusted based on the results of these tests.

5. Call your doctor at the start of any illness

In children with MMA+HCU, even minor illness could lead to serious health problems. In order to prevent problems, call your doctor right away when your child has any of the following:

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

When ill, your child needs extra fluids and carbohydrates to prevent more serious health problems. During an illness, you should restrict protein and give your child starchy foods and fluids.

Children with MMA+HCU may need to be treated in the hospital during illness. Ask your metabolic doctor if you should carry a special travel letter with medical instructions for your child's care.

What happens when MMA+HCU is treated?

Treatment may help some children but not others. Even with treatment, some babies and children may die. Others may have life-long learning problems or intellectual disabilities. Some children develop psychiatric disorders that are difficult to treat.

What causes the enzyme to be absent or not working correctly?

Genes tell the body to make various enzymes. People with MMA+HCU have a pair of genes that do not work correctly. Because of these gene changes, the needed enzyme does not work properly or is not made at all.

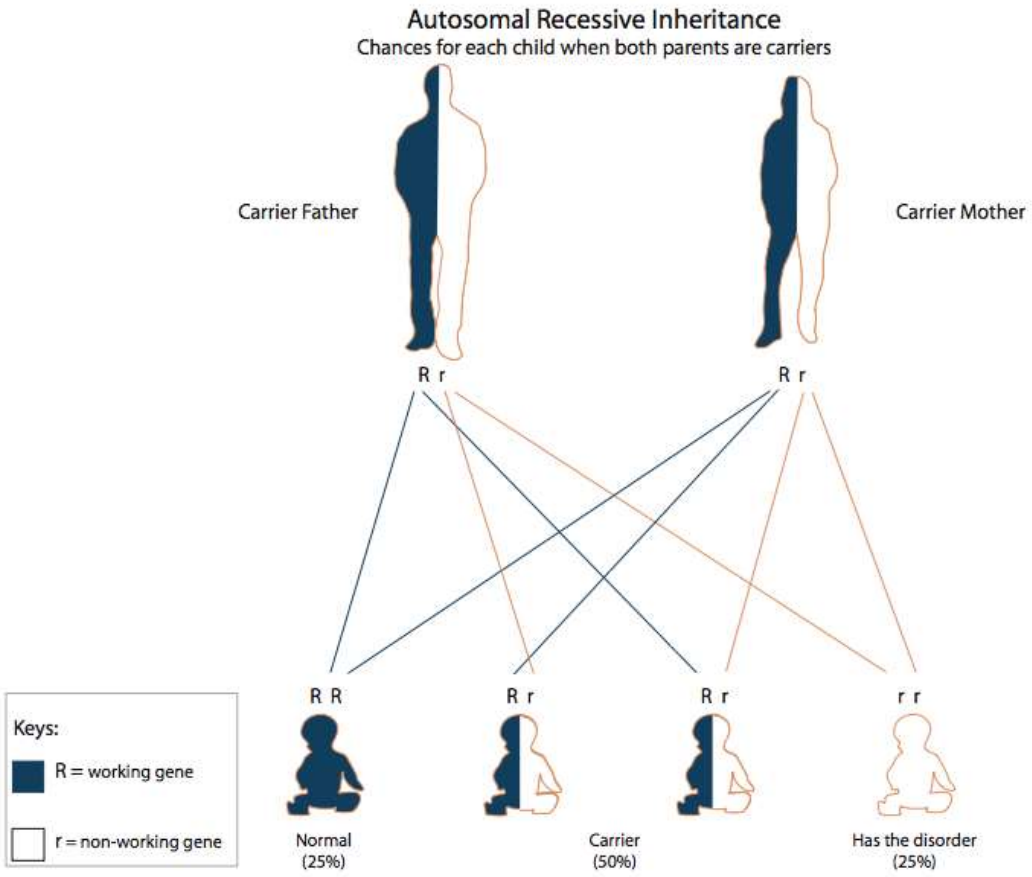
How is MMA+HCU inherited?

MMA+HCU is inherited in an autosomal recessive manner. It affects both boys and girls equally.

Everyone has a pair of genes that make the needed enzyme. In children with MMA+HCU, neither of these genes works correctly. These children inherit one non-working gene for the condition from each parent.

Parents of children with MMA+HCU rarely have the disorder. Instead, each parent has a single non-working gene for MMA+HCU. They are called carriers. Carriers do not have MMA+HCU because the other gene of this pair is working correctly.

When both parents are carriers, there is a 25% chance in each pregnancy for the child to have MMA+HCU. There is a 50% chance for the child to be a carrier, just like the parents. And, there is a 25% chance for the child to have two working genes.



Genetic counseling is available to families who have children with MMA+HCU. Genetic counselors can answer your questions about how MMA+HCU is inherited, choices during future pregnancies, and how to test other family members. Ask your doctor about a referral to a genetic counselor.

Is genetic testing available?

Genetic testing for MMA+HCU is available. Genetic testing, also called DNA testing, looks for changes in the pair of genes that cause MMA+HCU. Talk with your genetic counselor or metabolic doctor if you have questions about DNA testing.

DNA testing is not necessary to diagnose your child. However, if available, it can be helpful for carrier testing or prenatal diagnosis, discussed below.

What other testing is available?

Special tests on blood, urine, or skin samples can be done to help confirm MMA+HCU. Talk to your metabolic doctor or genetic counselor if you have questions about testing for MMA+HCU.

Can you test during pregnancy?

If both gene changes have been found in your child with MMA+HCU, DNA testing can be done during future pregnancies. The sample needed for this test is obtained by either CVS or amniocentesis.

If DNA testing would not be helpful, MMA+HCU can be detected by an enzyme test using cells from the fetus. The sample needed for this test is obtained by CVS or amniocentesis.

Parents may either choose to have testing during pregnancy or wait until birth to have the baby tested. A genetic counselor can talk to you about your choices and answer questions about prenatal testing or testing your baby after birth.

Can other members of the family have MMA+HCU or be carriers?

Having MMA+HCU

If they are healthy and growing normally, older brothers and sisters of a baby with MMA+HCU are unlikely to have the condition. However, finding out if other children in the family have this condition may be important because early treatment may prevent serious health problems. Ask your metabolic doctor whether your other children should be tested.

MMA+HCU carriers

Brothers and sister who do not have MMA+HCU still have a chance to be carriers like their parents. Except in special cases, carrier testing should only be done on people over 18 years of age.

Each of the parents' brothers and sisters has a 50% chance to be a carrier. It is important for other family members to be told that they could be carriers. There is a small chance they are also at risk to have children with MMA+HCU.

All states offer newborn screening for MMA+HCU. However, when both parents are MMA+HCU carriers, newborn screening results are not sufficient to rule out the condition in a newborn baby. In this case, special diagnostic testing should be done in addition to newborn screening.

Can other family members be tested?

Diagnostic testing

Brothers and sisters of a child with MMA+HCU can have special tests on blood, urine, or skin samples. Talk to your doctor or genetic counselor if you have questions about whether your other children should be tested for MMA+HCU.

Carrier testing

If the gene changes have been identified in your child with MMA+HCU, carrier testing can be done for other family members. If you have questions about carrier testing, ask your genetic counselor or metabolic doctor.

How many people have MMA+HCU?

This condition is thought to be very rare. The actual incidence is unknown. The most common form called methylmalonic acidemia with homocystinuria, cblC type, is estimated to affect 1 in 200,000 newborns worldwide.

Does MMA+HCU happen more frequently in a certain ethnic group?

MMA+HCU does not occur more often in any specific race, ethnic group, geographical area, or country.

Does MMA+HCU go by any other names?

MMA+HCU is also sometimes called:

- Combined deficiency of methylmalonyl CoA mutase and homocystinuria
- Methyltetrahydrofolate methyltransferase deficiency
- Vitamin B12 metabolic defect, Type 2
- Methylmalonic acidemia and homocystinuria
- Cbl C deficiency
- Cbl D deficiency
- Cbl F deficiency

Where can I find more information?

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

CLIMB (Children Living with Inherited Metabolic Disorders)
http://www.climb.org.uk

Save Babies Through Screening Foundation
http://www.savebabies.org/

Baby's First Test
http://www.babysfirsttest.org

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