Parents' Guide to MMA

Methylmalonic Acidemia

California
Department of
Health Services

Newborn Screening Program
Genetic Disease Branch
www.dhs.ca.gov/gdb

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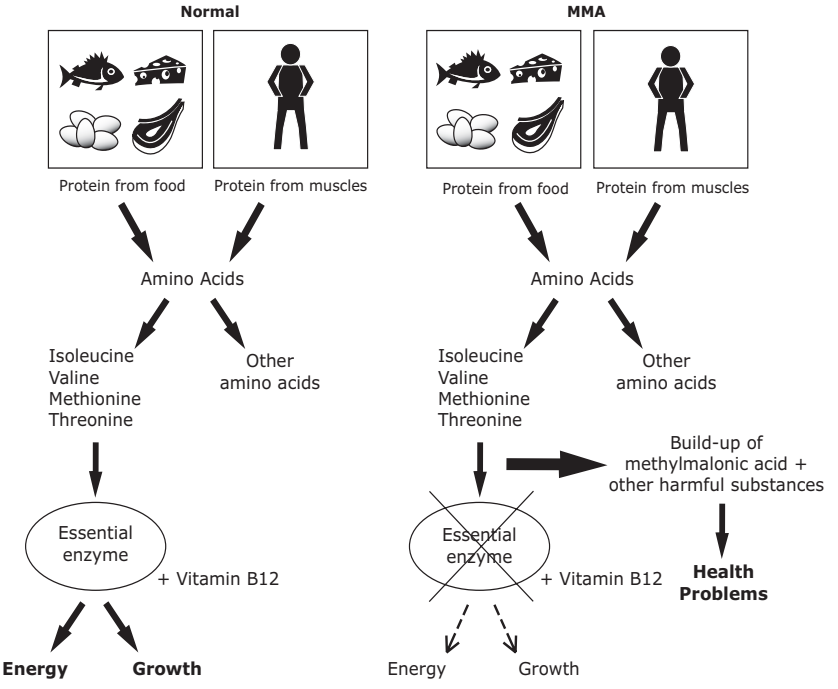
*Underlined words in booklet are defined in the Glossary

The information in this booklet is general and is not meant to be specific to each child with MMA. Certain treatments may be recommended for some children but not others. Children with MMA should be followed by a physician specializing in metabolic diseases (metabolic specialist) in addition to their primary doctor. For a list of metabolic centers, see page 22 or visit our website at: www.dhs.ca.gov/gdb.

What is MMA?

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



What causes MMA?

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 by enzymes into fatty acids that the body can use for energy.

MMA occurs when one of these special enzymes is either missing or not working properly. Without this enzyme, certain amino acids and fatty acids cannot be used correctly. This causes glycine, methylmalonic acid, and other harmful substances to build up in the blood and urine and cause health problems.

There are a number of different forms of MMA. Some forms can be treated with vitamin B12 injections. These types are called 'vitamin B12 responsive'. Two types of MMA that often can be treated with vitamin B12 are Cobalamin A (Cbl A) deficiency and Cobalamin B (Cbl B) deficiency.

There are other forms of MMA which cannot be treated with vitamin B12. These types are called ‘vitamin B12 non-responsive’. One of these is called ‘Mut 0’. It is caused by the absence of an enzyme called methylmalonyl-CoA mutase (MCM). Another type of MMA that does not respond to vitamin B12 treatment is called ‘Mut –’. People with the ‘Mut –’ type of MMA have too little of the MCM enzyme.

There is another form of MMA, called ‘MMA with homocystinuria’. For more information about this condition, please refer to the fact sheet developed by FELSI which is available on their website at www.newbornscreeninginfo/FELSI.

Isoleucine, valine, methionine, and threonine are the four amino acids that cannot be used correctly by people with MMA. These amino acids 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.

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

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

If MMA is not treated, what problems occur?

Each child with MMA is likely to have somewhat different effects. Many babies with MMA start having symptoms in the first few days of life. Others begin to show symptoms sometime in infancy or childhood. Some people with MMA never develop symptoms.

MMA causes episodes of illness called metabolic crises. Some of the first symptoms of a metabolic crisis are:

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

Common blood and urine findings are:

- ketones in the urine
- high levels of acidic substances in the blood, called metabolic acidosis
- high blood ammonia levels
- high blood and urine levels of glycine
- high blood and urine levels of methylmalonic acid and propionic acid
- high levels of other harmful substances
- low platelets
- low white blood cells
- anemia

If a metabolic crisis is not treated, a child with MMA can develop:

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

A metabolic crisis can be triggered by:

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

Between episodes of metabolic crisis, children with MMA may be healthy. However, some continue to have problems with health and development. Some children have long-term problems even if they have never had a metabolic crisis. These can include:

- learning disabilities or mental retardation
- delays in walking and motor skills
- abnormal involuntary movements (dystonia and choreoathetosis)
- rigid muscle tone, called spasticity
- poor growth with short stature
- skin rashes and infections
- osteoporosis
- enlarged liver
- kidney disease or failure

Without treatment, brain and nerve damage can occur. This can cause mental retardation and problems with involuntary movements. Death is common in untreated babies and children.

A small number of people with MMA never show symptoms.

What happens when MMA is treated?

Babies and children who have prompt and ongoing treatment may be able to live healthy lives with normal growth and development. In general, the earlier treatment is started, the better the outcome.

Children who respond to vitamin B12 treatment tend to do very well as long as treatment is continued. Children who are not treated until after they have symptoms may have lasting health and learning problems.

Even with treatment, some children develop life-long learning disabilities or mental retardation. In addition, despite treatment, seizures, involuntary movement disorders, and kidney failure have occurred in some children.

What is the treatment for MMA?

Your baby's primary doctor will work with a metabolic specialist and a dietician to care for your child.

Prompt treatment is needed to reduce the chance for mental retardation and serious medical problems. Children with 'vitamin B12 responsive' MMA are given vitamin B12. In addition, most children need to be on a low-protein diet and drink a special medical formula. You should start the treatments as soon as you know your child has MMA.

The following pages describe treatments often recommended for children with MMA.

1. Medication

The main treatment for 'vitamin B12 responsive' MMA is vitamin B12 injections in the form of hydroxocobalamin (OH-cbl) or cyanocobalamin (CN-cbl). Vitamin B12 injections can prevent symptoms in children with this form of MMA.

Over 90% of children with CblA deficiency respond to vitamin B12 injections. About 40% of children with CblB deficiency are helped by this treatment. Your doctors may need to treat your child with vitamin B12 for a short period of time to determine whether this treatment is useful.

Children with MMA 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.

Antibiotics taken by mouth can help lower the amount of methylmalonic acid made in the intestines. Your doctor will decide

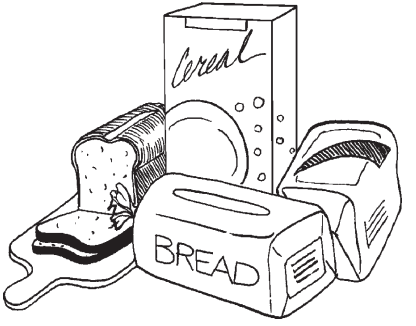
if your child needs antibiotics and, if so, what type.

Children who are having symptoms of a metabolic crisis should be treated in the hospital. During a metabolic crisis, your child may be given medications such as bicarbonate through an IV (intravenous) to help reduce the acid levels in the blood. Glucose is given by IV to prevent the breakdown of protein and fat stored in the body.

Do not use any medication without checking with your doctor.

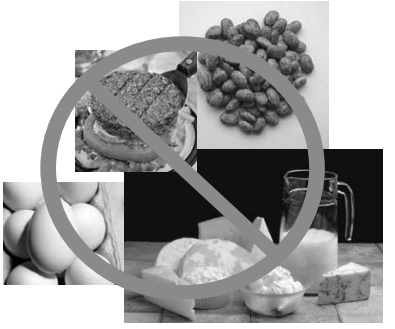
2. Low-protein diet, medical foods and medical formula

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:

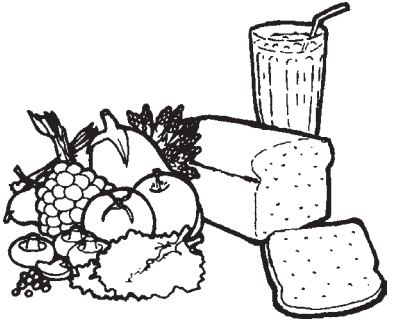
- milk and dairy products
- meat and poultry
- fish
- eggs
- dried beans and legumes
- nuts and peanut butter



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 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. It is likely your child will need to be on a special food plan throughout life.

In addition to a low-protein diet, your child may be given a special medical formula. This formula contains the correct amount of protein and nutrients your child needs for normal growth and development. Your metabolic specialist and dietician will tell you what type of formula 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.

3. Regular blood and urine tests

Periodic urine tests to check the level of ketones can be done at home or at the doctor's office. Ketones are substances formed when body fat is broken down for energy. This happens after going without food for long periods of time, during illness, and during periods of heavy exercise. Too many ketones in the urine may signal the start of a metabolic crisis.

Your child will have regular blood tests to measure the level of amino acids. Urine tests may also be done. Your child's diet and medication may need to be adjusted based on the results of these tests.

4. Call your doctor immediately if your child has signs of illness

For children with MMA, even minor illness could lead to a metabolic crisis. To prevent serious health problems, call your doctor right away when your child has any of the following symptoms:

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

When ill, your child needs extra fluids and carbohydrates in order to prevent a metabolic crisis. During an illness, you should restrict protein and give your child starchy foods and fluids. Children with MMA may need to be treated in the hospital during illness to avoid serious health problems.

5. Organ transplantation

Some children with MMA are given liver or kidney transplants, or both. This may reduce some of the symptoms. However, transplant surgery has serious risks and may or may not be right for your child. Talk with your doctor or metabolic specialist if you have questions about the risks and benefits of transplantation.

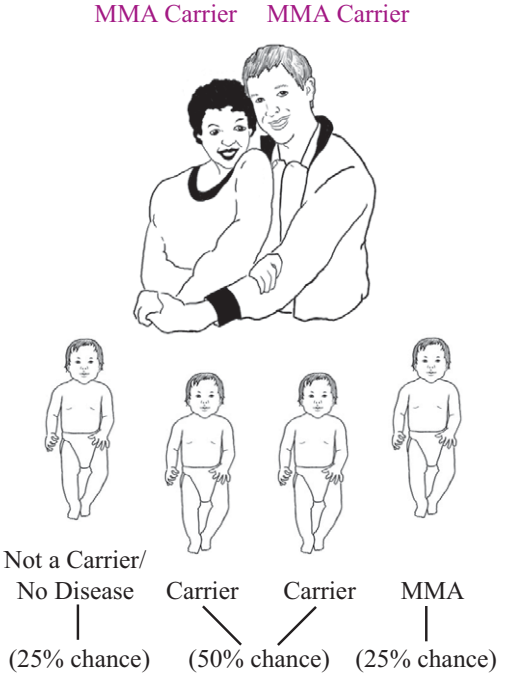
How is MMA inherited?

MMA affects both boys and girls equally.

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

Parents of children with MMA rarely have the disorder. Instead, each parent has a single non-working gene for MMA. They are called carriers. Carriers are not affected because their 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 two working genes. This means the child is not a carrier and does not have the disease. There is a 50% chance for the child to be a carrier, just like the parents. There is a 25% chance for the child to have MMA.



Genetic counseling is available to families who have children with MMA. Genetic counselors can answer your questions about how MMA is inherited, options during future pregnancies, and how to test other family members. Other family members can also ask about genetic counseling and testing for MMA.

Is genetic testing available?

Genetic testing for MMA may be possible. Genetic testing, also called DNA testing, looks for changes in the pair of genes that cause MMA. Talk with your genetic counselor or metabolic specialist if you have questions about DNA testing.

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

What other testing is available?

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

Can you test during pregnancy?

If both gene changes are known in your child with MMA, DNA testing can be done during future pregnancies to determine if the sibling also has MMA. The sample needed for this test is obtained by either CVS or amniocentesis.

MMA can also be found through an enzyme test using cells from the fetus. The sample needed for this test is obtained by 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 or be carriers?

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

Brothers and sisters who do not have MMA still have a chance to be carriers like their parents. Carriers do not have the disorder and will never develop it.

Each of the parents' brothers and sisters has a chance to be an MMA 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.

When both parents are known MMA carriers or have had a baby with MMA, subsequent newborns should have special diagnostic testing in addition to the newborn screen to test for MMA.

How many people have MMA?

About one in 48,000 babies in the United States is born with MMA. MMA occurs in all ethnic groups around the world. It does not occur more often in any specific race, ethnic group, geographical area, or country.

Does MMA go by any other names?

There are a number of different forms of MMA. The 'vitamin B12 non-responsive' forms are sometimes also called:

- Methylmalonic aciduria due to methylmalonic CoA mutase deficiency
- Complementation group Mut (includes Mut 0 and Mut -)
- Methylmalonyl CoA mutase deficiency
- MCM Deficiency

The vitamin B12 responsive forms are sometimes also called:

- Methylmalonic aciduria, Cbl A
- Methylmalonic aciduria, Cbl B
- MMAA/MMAB
- Adenosylcobalamin deficiency

Another type of MMA has additional symptoms of a separate condition called homocystinuria. This condition is also called:

- Methylmalonic acidemia (Cbl C, D)

RESOURCES

Organic Acidemia Association
13210 35th Avenue North
Plymouth, MN 55441
(763) 559-1797
www.oaanews.org

Children Living with Inherited Metabolic Disorders
CLIMB Building
176 Nantwich Road
Crewe, CS2 6BG
United Kingdom
www.climb.org.uk

Save Babies Through Screening Foundation
4 Manor View Circle
Malvern, PA 19355-1622
(888) 454-3383
www.savebabies.org

Genetic Alliance
4301 Connecticut Ave. NW, Suite 404
Washington, DC 20008-2369
(202) 966-5557
www.geneticalliance.org

CALIFORNIA METABOLIC CENTERS

Cedars-Sinai Medical
Center, Los Angeles
(310) 423-9914

Children's Hospital Central
California, Madera
(559) 353-6400

Children's Hospital &
Research Center, Oakland
(510) 428-3550

Children's Hospital
Los Angeles
(323) 660-2450

Children's Hospital of
Orange County, Orange
(714) 532-8852

Children's Hospital and
Health Center of San Diego
(619) 543-7800

Harbor/UCLA Medical Center
Torrance
(310) 222-3756

Kaiser Permanente - No. Cal.
(510) 752-7703

Kaiser Permanente - So. Cal.
(323) 783-6970

LAC/USC Medical Center
Los Angeles
(323) 226-3816

Lucile Salter Packard Children's
Hospital at Stanford
(650) 723-6858

Sutter Medical Center
Sacramento
(916) 733-6023

UC Davis Medical Center
(916) 734-3112

UC San Francisco Medical Center
(415) 476-2757

UCLA Medical Center
(310) 206-6581

UCI Medical Center, Orange
(714) 456-8513

GLOSSARY

Amniocentesis - Test done during pregnancy (usually between 16 and 20 weeks). A needle is used to remove a small sample of fluid from the sac around the fetus. The sample can be used to test for certain genetic disorders in the fetus.

Autosomal recessive - Autosomal recessive conditions affect both boys and girls equally. How autosomal recessive inheritance works: Everyone has a pair of genes responsible for making each enzyme in the body. A person with a metabolic disorder has one enzyme that is either missing or not working properly. The problem is caused by a pair of "recessive" genes that are not working correctly. They do not make the needed enzyme. A person has to have two non-working "recessive" genes in order to have an autosomal recessive metabolic disorder. A person with an autosomal recessive disorder inherits one non-working gene from their mother and the other from their father.

Bicarbonate - A substance that lowers the amount of acid in the blood. It is some times used as part of the treatment for children with certain organic acid disorders.

Carrier - A person who has a gene mutation in one of their genes that causes a disease, but does not have any symptoms of the disease themself. The mutation is often recessive, which means that both copies of the gene have to be mutated in order for disease symptoms to develop. Carriers are able to pass the mutation onto their children and therefore have an increased chance of having a child with the disease.

CVS - Chorionic Villus Sampling (CVS) is a special test done during early pregnancy (usually between 10 and 12 weeks). A small sample of the placenta is removed for testing. This sample can be used to test for certain genetic disorders in the fetus.

Cyanocobalamin - This is a form of vitamin B12 that can be given orally or by injection. This treatment increases the amount of vitamin B12 in the body. This is an important treatment for children with some forms of methylmalonic acidemia.

DNA - Deoxyribonucleic acid (DNA) is a molecule that makes up chromosomes. It is composed of four units (called bases) that are designated A, T, G, and C. The sequence of the bases spell out instructions for making all of the proteins in an organism. The instructions set for each individual protein is a gene. A change

in one of the DNA letters making up a gene is a mutation. In some cases, these mutations can alter the protein instructions and lead to disease. Each individual passes their chromosomes on to their children, and therefore passes down the DNA instructions. It is these instructions that cause certain traits, such as eye or hair color, to be inherited.

Enzyme - A molecule that helps chemical reactions take place. For example, enzymes in the stomach speed up the process of breaking down food. Each enzyme can participate in many chemical reactions without changing or being used up.

Gene - A segment of DNA that contains the instructions to make a specific protein (or part of a protein). Genes are contained on chromosomes. Chromosomes, and the genes on those chromosomes, are passed on from parent to child. Errors in the DNA that make up a gene are called mutations and can lead to diseases.

Genetic Counseling - Genetic counseling gives patients and their families education and information about genetic-related conditions and helps them make informed decisions. It is often provided by Genetic Counselors or Medical Geneticists who have special training in inherited disorders.

Glucose - A type of sugar made from the carbohydrates in food. Glucose is found in the blood. It is the main source of energy for the body and brain.

Hydroxocobalamin - A form of vitamin B12 that can be given by injection. These injections increase the amount of vitamin B12 in the body. This is an important treatment for children with some forms of methylmalonic acidemia.

Metabolic Crisis (Metabolic Crises = plural) - A serious health condition caused by low blood sugar and the build-up of toxic substances in the blood. Symptoms of a metabolic crisis are: poor appetite, nausea, vomiting, diarrhea, extreme sleepiness, irritable mood and behavior changes. If not treated, breathing problems, seizures, coma, and sometimes even death can occur. Metabolic crises happen more often in people with certain metabolic disorders. They are often triggered by things like illness or infection, going without food for a long time, and, in some cases, heavy exercise.

Organic Acid Disorders (OA) - A group of rare inherited conditions. OA disorders are caused by one or more enzymes that do not work properly. People with these conditions cannot digest certain parts of protein from the food they eat. This causes harmful substances to build up in their blood and urine. This can cause serious

effects on health, growth, and learning.

Osteoporosis - A condition that causes the bones to become thinner over time. People with this condition have a higher chance for bone fractures.

Seizure - Also called “convulsions” or “fits.” During a seizure, a person loses consciousness and control of their muscles. It may also cause involuntary movements. Seizures can happen for many reasons. Some causes are metabolic disorders, a metabolic crisis, brain injury, and infection.

Stroke - When the blood or oxygen supply to part of the brain is stopped. It can be caused by a blood clot or a leak in a blood vessel. It may cause loss of speech, language, and the ability to move certain body parts. If severe, it can cause death.

NOTES OR QUESTIONS FOR MY DOCTOR

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