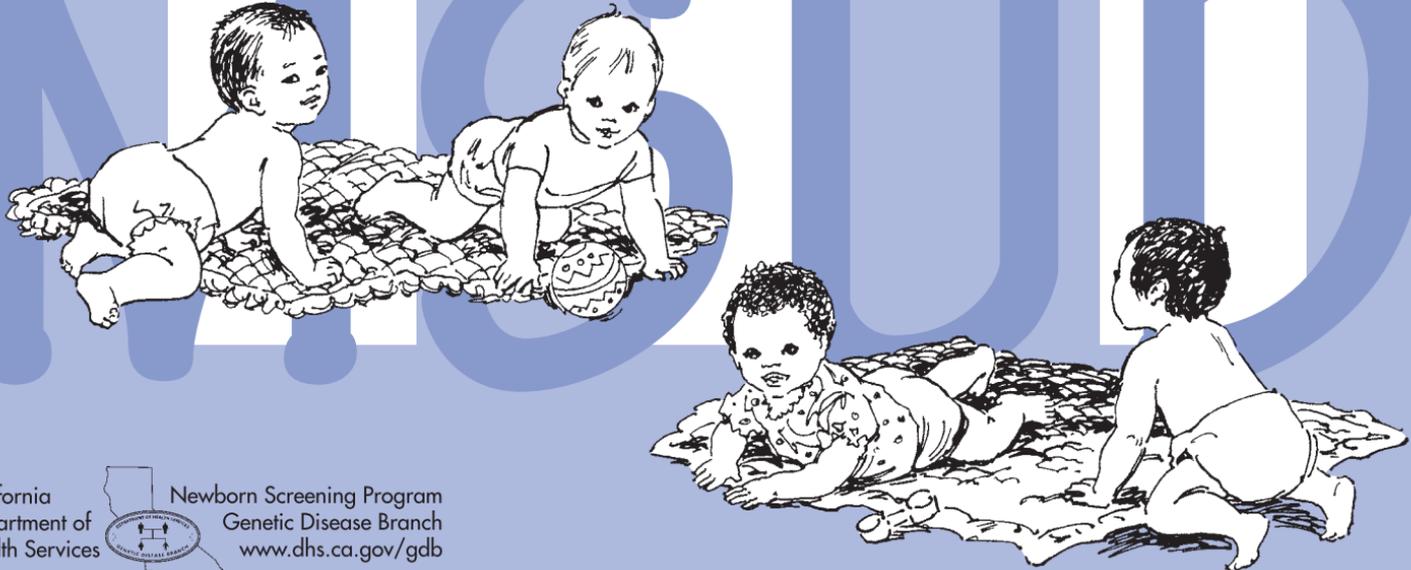


Parents' Guide to MSUD

Maple Syrup Urine Disease



California
Department of
Health Services



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

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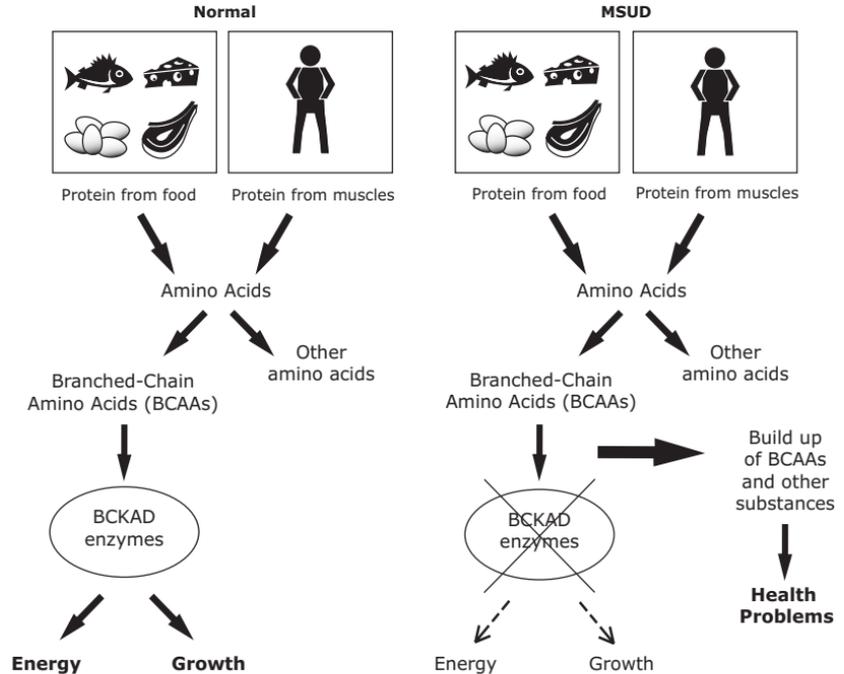
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The information in this booklet is general and is not meant to be specific to each child with MSUD. Certain treatments may be recommended for some children but not others. Children with MSUD should be followed by a physician specializing in metabolic diseases (metabolic specialist) in addition to their primary doctor. For a list of metabolic centers, see page 18 or visit our website at www.dhs.ca.gov/gdb.

*Underlined words in booklet are defined in the Glossary

What is MSUD?

MSUD stands for “maple syrup urine disease.” It is named for the sweet maple syrup smell of the urine in most untreated babies. This condition is one type of amino acid disorder. People with these disorders have problems breaking down amino acids from the protein in the food they eat. MSUD can also be classified as an organic acid disorder.



What causes MSUD?

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.

Classic MSUD, the most common form, is caused by the absence of a group of enzymes called “branched-chain ketoacid dehydrogenase” (BCKAD). The job of this enzyme group is to break down three different amino acids called leucine, isoleucine and valine. When they cannot be broken down, these amino acids build up in the blood and cause problems.

Leucine, isoleucine, and valine are called “branched-chain amino acids” (BCAAs) because of their “tree-like” structure. They are found in all foods that contain protein. Large amounts are found in meat, eggs, milk, and other dairy foods. Smaller amounts are found in flour, cereal, and in some vegetables and fruits.

What causes the BCKAD enzymes to be missing or not working correctly?

Genes tell the body to make various enzymes. People with MSUD have a pair of genes that do not work correctly. Because of these gene changes, the BCKAD enzymes do not work properly or are not made at all.

If MSUD is not treated, what problems occur?

There are a number of different forms of MSUD. The most common form, “classic MSUD”, can be life-threatening and must be treated promptly to prevent serious health problems. Other forms are less severe. These milder forms are less common. This booklet contains information on classic MSUD.

Classic MSUD

Symptoms usually start shortly after birth. Some of the first symptoms may include:

- poor appetite
- weak suck
- weight loss
- high pitched cry
- urine that smells like maple syrup or burnt sugar

Babies with MSUD have episodes of illness called metabolic crises.

Some of the first symptoms of a metabolic crisis are:

- extreme sleepiness
- sluggishness
- irritable mood
- vomiting

If not treated, other symptoms can follow:

- episodes where the muscles become tight and rigid and then go limp
- swelling of the brain
- seizures
- high levels of acidic substances in the blood, called metabolic acidosis
- coma, sometimes leading to death

Symptoms of a metabolic crisis often happen:

- after going too long without food
- during illness or infection
- during stressful events such as surgery

Without treatment, brain damage can occur. This can cause mental retardation or spasticity. Some babies become blind. If not treated, most babies die within a few months.

What happens when MSUD is treated?

With prompt and lifelong treatment, children with MSUD often have healthy lives with typical growth and development. Early treatment can help prevent brain damage and mental retardation.

Even with treatment, some children still develop swelling of the brain or have episodes of metabolic crisis. Children who have repeated metabolic crises may develop permanent brain damage. This can cause lifelong learning problems, mental retardation or spasticity.

What is the treatment for MSUD?

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

Prompt treatment is needed to prevent mental retardation and serious medical problems. Most children need to eat a very low-protein diet and drink a special medical formula. You should start



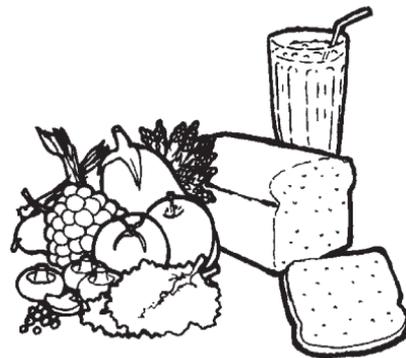
the diet and the formula as soon as you know your child has MSUD. Your dietician can create a food plan that contains the right amount of protein, nutrients, and energy to keep your child healthy.

The following are treatments often recommended for children with MSUD:

1. Medical Formula

In addition to a low-protein diet, children are often given a special medical formula as a substitute for milk. This formula gives them the nutrients and protein they need while helping keep their BCAA levels in a safe range.

Your metabolic specialist and dietician will tell you what type of formula is best and how much to use.



2. Diet low in branched-chain amino acids

The diet is made up of foods that are very low in the BCAAs. This means your child will need to avoid foods such as cow's milk, regular formula, meat, fish, cheese and eggs. Regular flour, dried beans, nuts, and peanut butter also have BCAAs and must be avoided or strictly limited.

Many vegetables and fruits have only small amounts of the BCAAs and can be eaten in carefully measured amounts.

There are other medical foods such as special low-protein flours, pastas, and rice that are made especially for people with MSUD.

Your metabolic specialist and dietician will decide on the best food plan for your child. The exact plan will depend on many things such as your child's age, weight, and general health. Your dietician will fine-tune the diet over time. Any diet changes should be made under the guidance of a dietician.



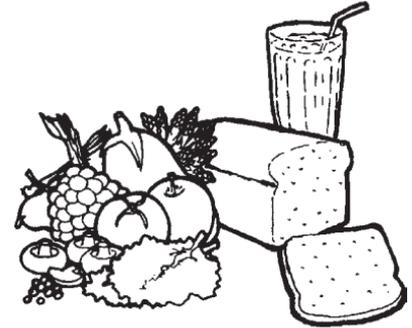
Lifelong treatment with the MSUD diet is necessary. Children are at risk for episodes of metabolic crisis when they don't follow the diet.

3. Tracking BCAA levels

Your child will have regular blood tests to measure amino acid levels. The diet and formula may need to be adjusted based on blood test results.

4. Supplements

Children with a rare form of MSUD, called “thiamine-responsive MSUD”, can often be helped by thiamine supplements. Some children with classic MSUD may also benefit from thiamine. Ask your doctor whether your child should take thiamine supplements. Do not use any supplements without checking with your doctor.



5. Call your doctor immediately at the sign of symptoms in your child

For children with MSUD, even minor illness can cause a metabolic crisis. In order to prevent problems, call your doctor right away when your child has any of the following:

- poor appetite
- low energy or extreme sleepiness
- vomiting
- an infection or illness
- a fever
- behavior or personality changes
- difficulty walking or balance problems

Children with MSUD need to eat more carbohydrates and drink more fluids during any illness – even if they're not hungry – or they could have a metabolic crisis. Children who are sick may not 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.



How is MSUD inherited?

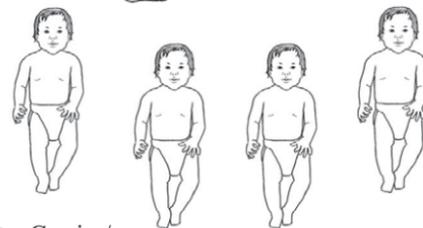
MSUD affects both boys and girls equally.

In children with MSUD, a pair of genes needed to make the BCKAD enzymes is not working correctly. These children inherit one non-working gene for MSUD from each parent. This is called autosomal recessive inheritance.

Parents of children with MSUD rarely have the condition themselves. Instead, each parent has a single non-working gene for MSUD. 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 MSUD.

MSUD Carrier MSUD Carrier



Not a Carrier/ No Disease	Carrier	Carrier	MSUD
(25% chance)	(50% chance)		(25% chance)

Chances apply to each pregnancy

Genetic counseling is available to families who have children with MSUD. Genetic counselors can answer your questions about how the condition 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 MSUD.

Is genetic testing available?

Genetic testing for MSUD can be done on a blood sample. Genetic testing, also called DNA testing, looks for changes in the pair of genes that cause MSUD.

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

What other testing is available?

MSUD can be confirmed by measuring the amount of the branched chain amino acids in a blood sample. It can also be diagnosed by



an enzyme test using a blood or skin sample. Talk to your doctor or genetic counselor if you have questions about testing for MSUD.

Can you test during pregnancy?

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

If DNA testing would not be helpful, an enzyme test can be done on cells from the fetus. Again, the sample needed for this test is obtained by either CVS or amniocentesis.

Parents may 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 MSUD or be carriers?

If they are healthy and growing normally, older brothers and sisters of a baby with MSUD are unlikely to have the condition. If you have questions about testing your other children, talk with your metabolic specialist or genetic counselor.

Brothers and sisters who do not have MSUD 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 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 MSUD.

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

How many people have MSUD?

About one in every 200,000 babies in the United States is born with MSUD.

Does MSUD happen more frequently in a certain ethnic group?

MSUD occurs in all ethnic groups. It is more common in Mennonite people in the United States. About 1 in 760 people of Mennonite background has MSUD. It is also more common in people of French-Canadian ancestry.

Does MSUD go by any other names?

MSUD is sometimes also called:

- branched chain ketoaciduria
- branched chain alpha-keto dehydrogenase deficiency
- BDKD deficiency

There are a number of other forms of MSUD that are less common than the classic type. These other forms are not discussed in this booklet:

- Intermittent branched-chain ketoaciduria
- Intermediate branched-chain ketoaciduria
- Thiamine responsive MSUD
- MSUD Type 1B
- MSUD Type II

RESOURCES

The MSUD Family Support Group
82 Ravine Road
Powell, Ohio
(740) 548-4475
www.msud-support.org

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

National Coalition for PKU and Allied Disorders
PO Box 1244
Mansfield, MA 02048
www.pku-allieddisorders.org

Children Living with Inherited Metabolic Disorders
CLIMB Building
176 Nantwich Road
Crewe, CW2 6BG
United Kingdom
www.climb.org.uk

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.

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. 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.

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.

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 (some fatty acid oxidation disorders, amino acid disorders, and organic acid disorders). They are often triggered by things like illness or infection, going without food for a long time, and, in some cases, heavy exercise.

Seizure - Also called “convulsions” or “fits.” During a seizure, a person may lose 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.

Spasticity - Rigidity of the muscles and increased reflexes. It is caused by increased muscle tone. It results in abnormal tightness or stiffness of the muscles and joints.

Thiamine - One type of B vitamin. Thiamine is found in grains, pork, beans, seeds and nuts. It plays a key role in changing food into energy.

NOTES AND/OR QUESTIONS FOR MY DOCTOR



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