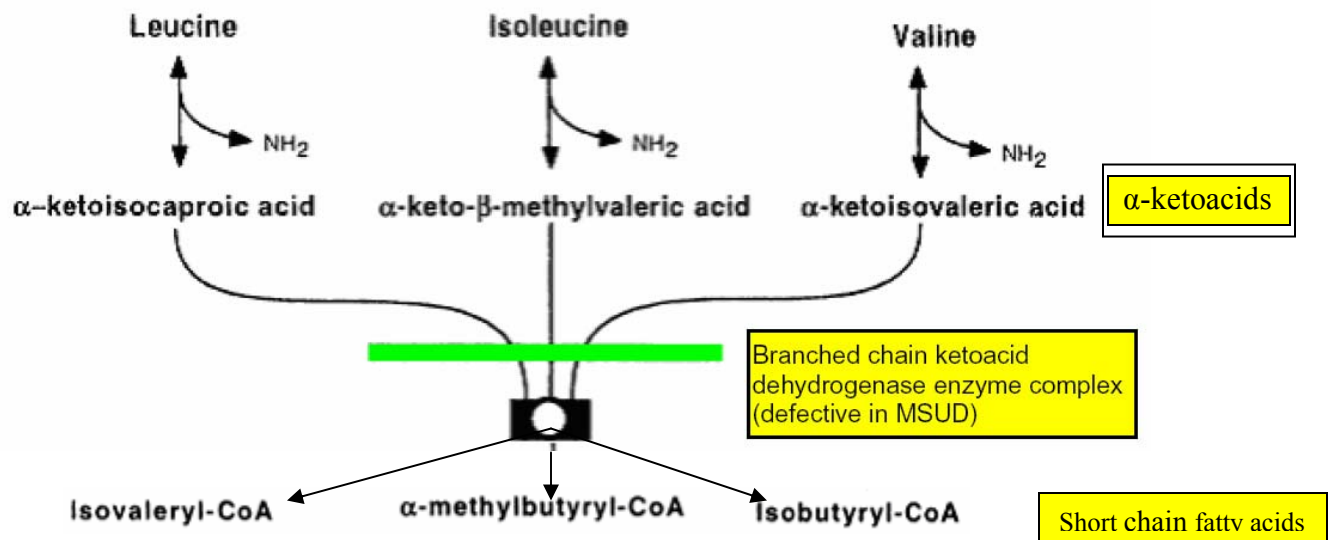


**Leucine mildly to moderately elevated, 153-305  $\mu\text{mol/L}$  with borderline elevated valine: Possible MSUD or hydroxyprolinemia**

MSUD is an inborn error of branched chain amino acids (BCAA) metabolism in which the  $\alpha$ -ketoacids derived from BCAA (leucine, isoleucine and valine) cannot be fully catabolized to their respective short-chain fatty acids because there is a deficiency of the branched chain ketoacid dehydrogenase complex (BCKD) (see diagram below). One or more of the branched chain  $\alpha$ -ketoacids (BCKA) that accumulate ( $\alpha$ -ketoisocaproic acid,  $\alpha$ -keto- $\beta$ -methylvaleric acid, and  $\alpha$ -ketoisovaleric acid) is (are) toxic. The major initial feature is encephalopathy and there may be a “maple syrup” or “burnt sugar” odor detectable in the cerumen in the ear or urine.



### History and examination

If the infant has any sign of illness or a markedly elevated leucine level, he/she must be seen by a metabolic physician the same day of notification from the newborn screening program. UNDER ANY CIRCUMSTANCE, A METABOLIC PHYSICIAN MUST BE CONSULTED.

### History

The neonate may have a normal history. The first symptoms include refusal to feed, lethargy and change in mental status.

### Examination

The infant may appear well. When symptomatic, the neonate with MSUD typically has the clinical picture of early encephalopathy and brain edema. Signs as subtle as poor Moro reflex are very concerning. The absence of maple syrup odor should not deter consideration of the diagnosis.

**ANY signs of illness must be treated as a medical emergency and treated immediately.**

**Go to Acute illness protocol, MSUD.**

**If the child appears well it is still essential to refer to the metabolic center to ensure that the child and family receive the necessary treatment and guidance to prevent morbidity. [Contact the metabolic physician for markedly elevated leucine](#)**

ENSURE THAT THE REPEAT NEWBORN SCREENING SAMPLE IS SENT TO THE NEWBORN SCREENING LABORATORY AND THE RESULT OBTAINED AS SOON AS POSSIBLE

(Go to [NNSGRC](#) for the state labs)

**[Discussion with parents for elevated leucine](#)**

## **Contact metabolic physician for markedly elevated leucine**

Your local metabolic physician can be found via [metabolic physicians and specialists](#)

The metabolic physician's role

- Provides you with information about MSUD.
- Discusses, in further detail, the meaning of the test result with the family.
- Starts appropriate [treatment](#).
- Provides supportive counseling for the family.
- Undertakes [definitive investigations](#).
- Provides genetic / prenatal counseling.
- Hospitalizes, if necessary, in a metabolic unit for acute illnesses and intensive care. These infants cannot be managed conservatively when they become ill. The threshold should be very low for hospitalization and for very close metabolic monitoring by a metabolic physician.

Return to [discussion with parents for elevated leucine](#)

Response to a reported newborn screening result must be undertaken in two parts:

- Initial contact with the family, often by phone, to inform them of the newborn screening result.
- Meeting with the family at the office.

### **Initial communication**

Many parents want to know what the result is testing positive for and are reassured if their doctor has knowledge of MSUD or has taken the time to find out about the condition when informing the family (see [commonly asked questions](#)).

Elevated leucine levels of 153-305  $\mu\text{mol/L}$  could mean that the infant has MSUD (maple syrup urine disease). What appears to be increased leucine, however, could be increased hydroxyproline, indicating hydroxyprolinemia, a benign disease. Increased leucine may also be a transient finding and not indicative of MSUD.

MSUD is a disease in which the BCAA (branched chain amino acids) cannot be fully metabolized (see diagram of pathway). TREATMENT is available to for this condition. The mainstay of treatment is prevention of illness with early treatment. It is essential that parents arrange to see a metabolic doctor as soon as possible.

### **In the office**

Many parents do not understand newborn screening or the need to treat their apparently healthy baby.

Parental anxiety will be high and it is important to reassure them that

- Treatment is available
- Failure to treat a baby with MSUD may result in mental retardation or life threatening illness that includes coma and death.

Treatment for MSUD is based on helping the body incorporate BCAA as building blocks and avoiding situations in which muscle proteins are broken down such as febrile illnesses or gastroenteritis. When the latter happens, the metabolic doctor must be contacted and involved to ensure that all the necessary metabolic tests and measures are carried out.

**Further counseling, treatment and a more detailed assessment and testing of the infant is required; therefore [contact metabolic physician for elevated leucine](#)**

## Commonly asked questions

### **1. What is MSUD?**

MSUD, also known as maple syrup urine disease, is an organic acid disorder caused by a defect in the metabolism of a specific group of amino acid called branched chain amino acids. The inability to completely metabolize these amino acids leads to a toxic build up of these and related acids in the body. This is often exacerbated when the body is stressed (e.g. newborn period, fasting, operations or infections). During these times the body breaks down its own proteins releasing these amino acids to supply needed energy and as a result, these toxins accumulate.

### **2. How and when will we know if my baby has MSUD?**

If your baby's newborn screening result showed a slightly to moderately elevated leucine level, he or she possibly has MSUD. However, your baby could have another disease known as hydroxyprolinemia which does not cause problems, or could have increased leucine as a transient finding of no consequence. The newborn screening test will be repeated and additional tests will be undertaken to help determine whether or not your baby has MSUD. The results of these tests may take up to 2 days to come back.

Depending on the test results, additional testing can take a variable amount of time to confirm the diagnosis. Very rarely, it can be difficult to determine whether or not your baby is affected.

### **3. How did my baby get this?**

MSUD is an autosomal recessive genetic disorder. This means that if your baby has MSUD, he/she has two abnormal mutated genes, one from the mother and one from the father. Each of you will have one mutated gene (a carrier). Being a carrier does not affect a person at all.

### **4. What does it mean for my child?**

If your baby has MSUD, he or she will have to be on a special protein restricted diet, and also take a special formula to ensure that the diet is adequate and balanced. If your child becomes ill, it may well be necessary early in the illness (i.e. when it might be considered mild), to further restrict the protein intake for a short period of time or even to provide extra energy in the form of glucose through additional sugar or, if necessary, by intravenous infusion. By treating your baby this way it is possible to generally prevent the worst effects of these conditions. However, babies and children with MSUD are at risk for learning disabilities, mental retardation, or even death if allowed to get sick and not receive the necessary immediate treatment. Therefore, it is important to maintain vigilance and consider every illness seriously. Some children, despite the best treatment and care possible, will still have some delay though this will be significantly less than if your child is not treated as described above.

### **5. What is the treatment? Does it work? Is the diet difficult to do/expensive?**

MSUD is primarily treated by a protein-restricted diet and special formula. The special formula, which will keep your child well, is typically ordered through your metabolic clinic where the metabolic nutritionist will ensure that you are confident in preparing it. Your metabolic clinic will assist you in obtaining the formula through your health care provider or state agency.

### **6. What about my other children/future children?**

As MSUD is an inherited condition it is essential to have your other children tested. Children from the same father and mother as the affected infant have a 1 in 4 (25%) chance of having the same condition. Your other children can appear healthy and still have the disorder. If they have MSUD, successfully having weathered illnesses in the past is no guarantee that an illness in the future will not have serious consequences. If they were not screened for MSUD when they were babies, they should be tested. Since there is a risk (1 in 4 or 25% in each pregnancy) for having a future child with MSUD it is important to let your obstetrician and pediatrician know that you have a child with MSUD if you are planning future pregnancies so that they may discuss the options with you and prepare accordingly.

## Definitive Investigations

### 1. Urine organic acids

In patients with MSUD there is an increase in the excretion of BCKA (branched chain  $\alpha$ -ketoacids) in the urine. DNPH (dinitrophenylhydrazine) test on urine is a simple and quick test that specifically detects BCKA. DNPH is particularly helpful when dealing with acute metabolic decompensation. However, urine organic acid analysis by quantitative or semi-quantitative techniques is far more sensitive and must be ordered.

### 2. Plasma amino acids

The profile of patients with MSUD is characterized by increased levels of leucine and, to a lesser extent, valine, isoleucine and alloisoleucine as determined by the amino acid analyzer. Prolonged fasting in the absence of MSUD can cause elevation of the BCAA (branched chain amino acids) but no alloisoleucine will be detected. Thus, alloisoleucine is considered pathognomonic for MSUD.

### 3. Acute laboratory tests

Acute management labs should take priority (blood glucose, blood gases, electrolytes, lactate, pyruvate, urinalysis for ketones). Diagnostic and follow up management labs during acute illness include urinalysis for ketones, urine for organic acids, and plasma amino acids. Consider DNPH testing of urine (if available). See [Acute illness protocol, MSUD](#).

### 4. Enzyme assay

BCKD (branched chain  $\alpha$ -ketoacid dehydrogenase) enzymatic activity can be measured in cultured fibroblast cells (e.g. from a skin biopsy). [Go to genetests](#)

### 5. Molecular testing

Specific mutations in MSUD have been identified for MSUD in the BCKD (branched chain  $\alpha$ -ketoacid dehydrogenase) gene. [Go to genetests](#) to determine if molecular testing is being offered.

## Treatment

### Diet

The mainstay in treatment of MSUD, including the immediate acute neonatal illness, is to enhance anabolism, prevent catabolism and restrict intake of BCAA. Specifically this entails providing adequate calories and limiting protein intake. The three BCAA are essential amino acids i.e. cannot be synthesized in the body and have to be supplied in the diet. Therefore, even though BCAA-free diet is recommended during acute metabolic

decompensation, one has to follow levels of BCAA closely. Typically, isoleucine and valine drop precipitously relative to leucine so they need to be reintroduced as soon as this happens, typically within 48-72 hours. Failure to provide the minimum requirement of BCAA can result in stunted growth and, in the case of isoleucine, and perhaps also valine, severe skin rash akin to that seen in acrodermatitis enteropathica. Fortunately, the latter complication responds very quickly to dietary adjustment.

#### **Acute illness treatment**

See [Acute illness protocol](#).