Carnitine Palmitoyl Transferase Deficiency Type 1-A

(CPT-1A**,** CPT deficiency, Liver form of carnitine palmitoyltransferase deficiency, Hepatic CPT 1)

Technical advisory committee report

Note: this disorder is not included in the recommended panel, however, the Technical Committee felt that it should be considered for Washington because of a high frequency reported among one Alaskan and one Canadian native group. Also note, however, that native groups account for a very small (less than 2%) portion of Washington births, and the majority of these are from local tribes.

Treatment

Treatment is relatively simple and effective at preventing mortality and at least some morbidity.

Available Technology – Screen

The screening test is probably effective at detecting affected infants. There are questions about false positives. Diagnosis may be difficult in the general population, however, the native cases have all been associated with a single mutation. Thus DNA testing is highly effective for confirming the diagnosis in these infants. Oregon's experience in screening Alaska's babies is that they identify more cases from the 2nd screen than from the 1st.

Other

High rates found among the Yupic and Athabascan peoples of Alaska and Canada.

Concordance with Treatment and Screening Technology criteria:

Most concordance

Estimated frequency

Less than 1 in 100,000 births (general population, much higher in some ethnic groups)

Disorder family: fatty-acid oxidation

Primary screening analyte: [C0/(C16+C18)] (Fingerhut, Roschinger et al. 2001)

Secondary screening analytes: none

Variability in clinical presentation:

"'Classic CPT1' is a rare, serious disorder; babies with this deficiency cannot make the CPT enzyme at all. A mild form of CPT1 is common among Alaska Natives and Canadian Native peoples. Most Alaska Native babies with CPT1 can make 10-25% of the normal amount of the CPT enzyme." (Alaska)

"There are two distinct tissue-specific isoforms of the enzyme: the liver-type isoform (CPT-1A) and the muscle-type isoform (CPT-1B)." "To date, there has been no report of a patient with CPT-IB deficiency." (Fingerhut, Roschinger et al. 2001)

Burden if untreated:

"Children with CPT-1 deficiency usually present with life-threatening attacks of fasting hypoketotic hypoglycemia and coma during the first 2 years of life. Persistent neurologic deficits are common" (Fingerhut, Roschinger et al. 2001)

Babies with the mild form of CPT-1 may or may not experience similar outcomes if untreated. (no data available)

Efficacy of treatment/benefits of early intervention:

"This disorder is potentially fatal, if the metabolic perturbations of hypoglycemia or hyperammonemia go unrecognized. The prognosis is dependant on prompt management of the above complications. (Prasad, Johnson et al. 2001)

"Early detection of CPT-I by newborn screening might prevent both a neonatal life-threatening metabolic decompensation and commonly observed neurologic deficits." (Fingerhut, Roschinger et al. 2001)

Of six affected individuals in the Hutterite population: "Two patients have significant neurological impairment due to severe recurrent hypoglycemic crises. The remaining four patients with earlier detection and treatment have near normal outcomes." (Prasad, Johnson et al. 2001)

Unintended consequences of screening:

Identification of asymptomatic individuals, "Some children with CPT-1A deficiency have never had symptoms and are only found to be affected after a brother or sister has been diagnosed" (STAR-G 2006)

Miscellaneous

CPT-1A is common in the Inuit - Alaskan Natives, and Hutterite populations.

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Medical Care and Medicines:

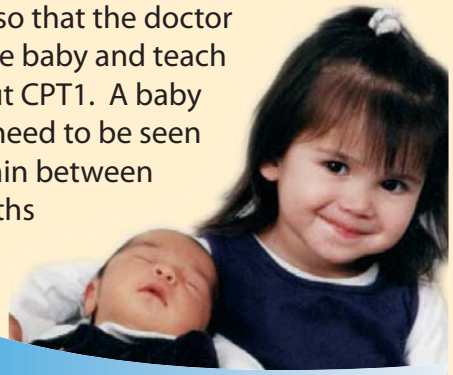
Your baby or child with CPT1 can have medications, medical care, or surgery as needed to stay healthy. If your baby or child needs surgery, IV fluids will be started before surgery and continue until the surgery is over and your baby or child is able to eat again.

Genetics of CPT1:

CPT1 is inherited. A baby with CPT1 has inherited two CPT genes -- one from the mother and one from the father. Brothers and sisters of a baby with CPT1 may have inherited this also. If other children in the family were born before October 2003, ask your doctor to test them for CPT1. This can be done by a cheek brush or dried blood spot at the pediatric clinic.

Metabolic Clinic:

CPT1 deficiency is a newly recognized condition. Doctors are still learning about why some children with CPT1 have mild problems and others have severe problems. Every baby with CPT1 needs to attend the metabolic genetics clinic before 6 months of age so that the doctor can examine the baby and teach the family about CPT1. A baby with CPT1 will need to be seen at the clinic again between 12 and 18 months of age.



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This brochure was funded in part by the Western States and Territories Genetic Services Collaborative.
Health Resources and Services Administration (HRSA) Grant # 1 U22MC03961-01-00. It was designed by the Alaska Genetics Clinic, Division of Public Health and printed at a cost of $___ per copy in Anchorage AK.

CPT1 Deficiency

Carnitine Palmitoyl Transferase Deficiency

CPT (Carnitine palmitoyl transferase) is an enzyme in the body that determines how a person can convert fat to energy. "CPT1 deficiency" happens when one enzyme used to break down fat is missing or not working properly.

In Alaska, every baby is tested for CPT1 as part of the newborn screening test. "Classic CPT1" is a rare, serious disorder; babies with this deficiency cannot make the CPT enzyme at all. A mild form of CPT1 is common among Alaska Natives and Canadian Native peoples. Most Alaska Native babies with CPT1 can make 10-25% of the normal amount of the CPT enzyme.

Treatment:

Ten to 25% of enzyme activity is enough for a baby to maintain good health, if the baby eats frequently. Babies with mild CPT1 are as healthy and normal as other babies. However, if a baby with mild CPT1 does not eat for more than 8 hours, he/she can get sick very quickly and develop seizures and coma.

Guidelines for Feeding Your Baby with mild CPT1

Newborn to 6 months old:

Feed your baby every 3-5 hours. The amount of breast milk or formula your baby needs is the same as other babies. It is important to feed your baby regularly every 3 to 5 hours.

- If your baby won't eat for two feedings, take your baby to the health aide to be sure that your baby does not have a fever or other illness that can be treated.
- Don't wait until your baby gets sick; talk with the health aide and be sure that your baby is safe.
- If your baby hasn't eaten for 8 hours, the health aide will arrange for the baby to go to the hospital. Your baby cannot go longer than 12 hours without food or IV fluids without becoming very ill.

6 to 12 months old:

As he/she grows, your baby will change how often and how much he/she wants to eat. Space meals 4 to 6 hours apart. Let your baby sleep for 6 to 8 hours at night.

- Be sure that your baby is breast fed or has formula or a snack before he/she goes to bed and be sure that your baby has breakfast as soon as he/she gets up each morning.
- During the day, offer your baby cereal, fruits, and vegetables. Begin to use a cup.
- Illness: If your baby refuses to eat two meals, has a fever, or vomits, take your baby to the health aide.
- If your baby hasn't eaten for 8 hours, the health aide will arrange for the baby to go to the hospital. Your baby cannot go longer than 12 hours without food or IV fluids without becoming very ill.

Over 1 year old:

Your child can space his meals 6-8 hours apart. Offer your child three meals and three snacks each day at regular times. Be sure that your child has breakfast and a bedtime snack.

- Your child does not need more food than other children his age. Your child needs small amounts of food at regular times each day. Do not force your child to eat when he is well.
- If your child is ill and hasn't eaten for 12 hours, the health aide will arrange for him/her to go to the hospital. Meanwhile try to have the child sip some juice or drink something with sugar in it.

3-hydroxy-3-methylglutaric aciduria

(HMG; 3-hydroxy-3-methylglutaryl-CoA lyase deficiency;
HMG CoA lyase deficiency; HL deficiency)

Technical advisory committee report

Treatment
Early detection and treatment is very effective in preventing clinical manifestations and death.

Available Technology - Screen
Screening test is effective at identifying affected infants (good sensitivity). However, screening test is also positive for infants with another disorder on the recommended list: 3-methylcrotonyl-CoA carboxylase (3MCC) deficiency, a disorder with uncertain clinical significance, so diagnostic differentiation is important. The screening test is also positive for two other disorders that were not included in the recommended panel that have uncertain clinical manifestations and treatment efficacy.

Concordance with Treatment and Screening Technology criteria:
Most concordance

Estimated frequency
1 in 100,000

Disorder family: fatty-acid oxidation/organic acidemia

Primary screening analyte: C5OH (same as 3MCC) (Zytkovicz, Fitzgerald et al. 2001)

Secondary screening analytes: C6DC (Zytkovicz, Fitzgerald et al. 2001)

Variability in clinical presentation:

Neonatal, infantile and childhood presentations. (Sweetman and Williams 2001)

Thirty of 62 patients presented in the first week of life – most of the others presented before one year of age. (Mitchell and Fukao 2001)

"Reports of asymptomatic individuals detected because of an affected sibling." (2006)

Burden if untreated:

"Vomiting, hypotonia, lethargy, coma, acidosis and hyperammonemia, hypoglycemia without ketosis" (Sweetman and Williams 2001)

Death in ~20 % of patients. (2006)

"Risk of mental retardation and epilepsy exceeds that expected in other conditions for similar lengths of time and severity of hypoglycemia." (Mitchell and Fukao 2001)

Efficacy of treatment/benefits of early intervention:

"We have encountered no symptomatic crises following diagnosis." (Mitchell and Fukao 2001)

"Significant prevention of mortality." (2005)

Unintended consequences of screening:

Three other disorders have elevated C5OH or 2-methyl-3-hydroxybutyrylcanitine (same mass in MS/MS). (Chace, Kalas et al. 2003)

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last modified: 9/7/2007

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency (HMG)

What is HMG?

HMG is a type of organic acid disorder. People with this condition have problems breaking down an amino acid called leucine from the food they eat.

What Causes HMG?

Enzymes help start chemical reactions in the body. HMG happens when an enzyme called "HMG CoA lyase" is either missing or not working well. This enzyme has two jobs. The first is to help break down leucine. All foods with protein contain leucine. The second job is to help the body make something called "ketone bodies" from stored fat.

What Symptoms or Problems Occur with HMG?

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

HMG causes periods of illness called Metabolic Crises. Some of the first symptoms are:

- poor appetite
- too much sleepiness or lack of energy
- irritable mood/behavior changes (such as crying for no reason)
- muscle weakness

Other problems then follow:

- fever
- diarrhea
- vomiting
- hypoglycemia (low blood sugar)
- increased levels of acid matter in the blood, called metabolic acidosis
- high levels of ammonia in the blood
- enlarged liver

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

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

When not treated, many babies die during their first Metabolic Crisis. Babies who live may have repeated Metabolic Crises that can cause brain damage. This can result in life-long learning problems or mental retardation and a seizure disorder.

Other problems can include:

- Heart enlargement
- Pancreatitis (inflamed pancreas gland)
- Hearing loss
- Vision problems

What is the Treatment for HMG?

The following treatments are often used for babies and children with HMG:

1. **Do not go a long time without food** – Babies and young children need to eat often to avoid a Metabolic Crisis. Most babies should not go without food for more than 4 to 6 hours. Some babies may need to eat more often. It is important to feed babies during the night. They may need to be woken to eat if they don't wake up on their own.

2. **Low-leucine diet, including medical foods and formula** – A food plan low in leucine that limits fat and protein is often part of the treatment. High-protein and high-fat foods that your child may need to limit or not eat at all include:

- milk and milk products
- meat and poultry
- fish
- eggs
- dried beans and peas
- nuts and peanut butter
- butter, margarine, oil, lard, and foods made with these fats

3. **Medications** – Taking L-carnitine may help some children. This is safe and natural and helps the body make energy. Use only the form prescribed by your doctor.

Things to Remember

Even minor illnesses such as a cold or the flu can cause a Metabolic Crisis. Call your doctor right away when your child has any of the following:

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

Children who are sick often don't 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.

β-ketothiolase deficiency

(BKT; mitochondrial acetoacetyl-CoA thiolase deficiency;
3-ketothiolase deficiency; 3-oxothiolase deficiency;
ketone utilization disorder; T2 deficiency;
2MeAcAc-CoA thiolase deficiency)

Technical advisory committee report

Treatment
Clinical presentations vary considerably from asymptomatic to fatal. Early identification and treatment is very effective at preventing death and developmental consequences.

Available Technology - Screen
The screening test is effective at detecting affected infants (good sensitivity) and does not have excessive false positives.

Concordance with Treatment and Screening Technology criteria:
Most concordance

Estimated frequency
1 in 100,000 births

Disorder family: organic acidemia

Primary screening analyte: C5:1 (Zytkovicz, Fitzgerald et al. 2001)

Secondary screening analytes: C5OH (Zytkovicz, Fitzgerald et al. 2001)

Variability in clinical presentation:

"There is great clinical heterogeneity in T2 deficiency." (Mitchell and Fukao 2001)

"Some patients tolerate normal protein intake." (Mitchell and Fukao 2001)

Documented asymptomatic siblings of patients. (Mitchell and Fukao 2001)

Burden if untreated:

Of 40 patients in literature – 10% died. Of survivors, 28% had some degree of mental retardation and 11% had poor weight gain. (Mitchell and Fukao 2001)

Efficacy of treatment/benefits of early intervention:

First episode usually 5 -24 months of age. (Mitchell and Fukao 2001)

"A favorable outcome is frequent if the first ketoacidotic crisis is rapidly diagnosed and treated." (Mitchell and Fukao 2001)

Unintended consequences of screening:

2-methyl-3-hydroxyacyl-CoA dehydrogenase (MHBD) deficiency has similar organic acid profile. (Fukao 2001)

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last modified: 8/25/2006

Beta Ketothiolase Deficiency
(BKD)

What is BKD?

BKD is a type of organic acid disorder. People with BKD can't break down an amino acid called isoleucine from the food they eat.

What Causes BKD?

Enzymes help start chemical reactions in the body. BKD happens when an enzyme called "mitochondrial acetoacetyl-CoA thiolase" (MAT) is missing or not working. This enzyme helps break down the amino acid isoleucine. All foods with protein contain isoleucine. Harmful matter can build up in the blood and cause problems when someone with BKD eats protein.

What Symptoms or Problems Occur with BKD?

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

BKD can cause periods of illness called Metabolic Crises. Some of the first symptoms of a Metabolic Crisis are:

- too much sleepiness or lack of energy
- vomiting and diarrhea
- fever
- poor appetite
- ketones in the urine

Later problems can include:

- mental retardation
- dystonia (muscle spasms)
- enlarged heart
- low blood platelets
- higher risk for infections
- not growing well
- kidney problems

What is the Treatment for BKD?

The treatments often recommended for babies and children with BKD are:

1. **Medication** – The doctor may prescribe L-carnitine for your child. This is safe and natural and helps the body make energy. It also helps the body get rid of harmful wastes.
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. Your doctor will tell you how to space your child's meals. Most healthy children over the age of 10 can go without food for up to 12 hours without problems.
3. **Low-protein diet** – Some children will need to eat a low-protein diet. High-protein foods to be limited include:

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

Children with BKD need some protein to grow properly. A dietitian can make a food plan for your child. Dietitians know what are the correct foods to eat.

Things to Remember

Even minor illness such as a cold or flu can lead to 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

An ill child with BKD needs more liquids, starchy foods (such as rice, cereal, bread), and sugars to avoid a Metabolic Crisis. When your child is ill, you will also need to limit protein.

Children with symptoms of a Metabolic Crisis need to be treated in a hospital.

Holocarboxylase synthase deficiency*
(HCSD)

* The ACMG report recommends screening for multiple carboxylase deficiency, which is broken down into an early-onset form (HCSD) and a later-onset form (biotinidase deficiency).

Technical advisory committee report

Treatment
Treatment is inexpensive, simple (vitamin supplement), and highly effective at preventing morbidity (mortality is not associated with this condition).

Available Technology - Screen
Screening test is very good at detecting affected infants (good sensitivity). However, the test is also positive for infants with any of three other conditions on the recommended list (the two forms of methylmalonic academia (mutase deficient and Cbl A,B), and propionic academia).

Concordance with Treatment and Screening Technology criteria:
Intermediate concordance

Estimated frequency
1 in 93,000 births

Disorder family: organic acidemia

Primary screening analyte: C3 (Zytkovicz, Fitzgerald et al. 2001)

Secondary screening analytes: C5OH (Zytkovicz, Fitzgerald et al. 2001)

Variability in clinical presentation:

Early-onset form: generally holocarboxylase synthetase deficiency. Age of onset: a few hours after birth to 21 months of age; most present before three months of age. (Wolf 2001)

Late-onset form: generally deficient activity of biotinidase. (Wolf 2001)

Burden if untreated:

"The most common initial clinical feature was tachypnea or another breathing difficulty. Other common symptoms … included feeding difficulties, hypotonia, seizures, lethargy, coma, and developmental delay." Coma and developmental delay present in between 10 and 25 percent of affected children. (Wolf 2001)

"Episodes of ketoacidosis evolving in dehydration and coma." (2005)

Efficacy of treatment/benefits of early intervention:

"All patients with holocarboxylase synthetase deficiency have responded to vitamin therapy." (Wolf 2001)

Unintended consequences of screening:

C3 is the primary analyte for three other conditions (MMA CblA,B; MMA mut; PROP). C5OH is a secondary analyte for BKT. (Zytkovicz, Fitzgerald et al. 2001)

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last modified: 8/25/2006

Multiple Carboxylase Deficiency
(MCD)

What is MCD?

MCD is an organic acid disorder. People with MCD can't change protein and carbohydrates from the food they eat into energy for the body.

What Causes MCD?

Enzymes help start chemical reactions in the body. The enzyme holocarboxylase synthetase (HCS) adds the vitamin biotin to other enzymes called "carboxylases." These change the food we eat into energy. Harmful matter builds up in the blood and urine when the HCS enzyme doesn't work. This can cause serious health problems.

What Symptoms or Problems Occur with MCD?

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

MCD causes periods of illness called Metabolic Crises. Some of the first symptoms are:

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

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

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

Later problems can include:

- mental retardation
- skin rash and hair loss
- unsteady movements
- rigid movement
- vision and hearing loss

What is the Treatment for MCD?

Biotin is usually the only treatment for MCD. Your doctor will prescribe the right amount. This will prevent symptoms in your child. It may rid your child of health problems when symptoms already exist. Early treatment prevents mental retardation and other serious medical problems. Treatment should start as soon as you know your child has MCD. Your child will need to take biotin for life.

Things to Remember

Babies who get treatment before they have a Metabolic Crisis usually have normal growth and development.

Some children develop learning problems even when treated. Children may also develop mental retardation. Treatment may not help the problems that already exist.

Carnitine uptake deficiency (systemic)

(CUD; Carnitine transporter defect; CTD; Systemic carnitine deficiency; SCD; Primary carnitine deficiency; plasma membrane carnitine Transporter defect, OCTN2 deficiency)

Technical advisory committee report

Treatment
Identification and treatment before the onset of symptoms is very effective in preventing death and disability.

Available Technology – Screen
The screening test will not identify all affected infants (moderate sensitivity). Also, sick infants often have false positive test results (low specificity).

Other
It is not urgent to treat right away so it may be beneficial to wait for results from the routine second screening specimen.

Concordance with Treatment and Screening Technology criteria:
Intermediate concordance

Estimated frequency
1 in 92,000 births

Disorder family: fatty-acid oxidation

Primary screening analyte: low C0 (Wilcken, Wiley et al. 2001; Schulze, Lindner et al. 2003)

Secondary screening analytes: total acylcarnitines (Schulze, Lindner et al. 2003)

Variability in clinical presentation:

Two clinically different forms have been described:

Early onset, "acute episodes of hypoglycemia and coma induced by fasting" (Stanley, Treem et al. 1990)

Late onset, "a more chronic course of progressive hypertrophic cardiomyopathy and skeletal muscle weakness. Hypoglycemia as a presenting manifestation has occurred in young infants under 1—2 years, whereas older infants, 2—7 years old, have more commonly presented with myopathy." (Stanley, Treem et al. 1990)

"In one family, one sib presented with hypoglycemia and the second with cardiomyopathy and weakness. These differences in mode of presentation probably reflect the chance occurrence of an episode of fasting long enough to cause hypoglycemia before the myopathy has become apparent." (Stanley, Treem et al. 1990)

Burden if untreated:

"Several instances of death from cardiac failure in patients prior to diagnosis have been seen, suggesting that OCTN2 deficiency is eventually fatal if not treated. (Stanley 2004)

Efficacy of treatment/benefits of early intervention:

"patients with this disorder respond dramatically to carnitine therapy." (Roe and Ding 2001)

"Treatment with oral carnitine at pharmacologic levels is quite effective in correcting the cardiomyopathy and muscle weakness in these children. Several children have survived into their third decade and appear to be doing well, even though carnitine treatment raises muscle carnitine concentrations to only 5—10% of normal." (Stanley 2004)

Unintended consequences of screening:

"In neonates, low free carnitine levels are seen principally in those who are sick. We found, in intensive care units, an over-representation of babies with levels <10 μmol/L (0.16 mg/dL)." (Wilcken, Wiley et al. 2001)

"We have shown that some cases of the carnitine transporter defect can be detected by expanded newborn screening. However, at least one and perhaps two of our clinically identified patients could not have been identified by measurement of free carnitine alone with any reasonable protocol." (Wilcken, Wiley et al. 2001)

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last modified: 8/25/2006

Carnitine Uptake Deficiency (CUD) or Carnitine Transport Deficiency (CTD)

What is CUD?

CUD is a kind of fatty acid oxidation disorder. People with CUD have problems breaking down fat into energy for the body.

What Causes CUD?

Enzymes help start chemical reactions in the body. CUD happens when an enzyme called "carnitine transporter" is either missing or not working right. This enzyme helps carry something called carnitine into our cells. Carnitine helps the body make energy from fats in food. It also helps us to use the fat that is already stored in the body.

What Symptoms or Problems Occur with CUD?

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

Babies with CUD first show signs of it between birth and age three. CUD can cause periods of illness called Metabolic Crises. Some of the first symptoms of a Metabolic Crisis are:

- too much sleepiness
- behavior changes (such as crying for no reason)
- irritable mood
- poor appetite

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

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

Repeated Metabolic Crises can cause brain damage. This can cause learning problems or mental retardation. CUD can also cause an enlarged heart and weak muscles.

What is the Treatment for CUD?

The following treatments are often used for children with CUD:

1. **L-carnitine** – The doctor usually prescribes the life-long use of L-carnitine. This is safe and natural and helps the body make energy. It also helps the body get rid of harmful wastes. L-carnitine can get rid of heart problems and muscle weakness in children with CUD.
2. **Do not go a long time without food** – Babies and young children with CUD should eat more often to avoid problems. They should not go without food for more than 4 to 6 hours. Some babies may need to eat even more often than this. It is important that babies be fed during the night. They need to be woken to eat if they do not wake up on their own.
3. **Diet** – Sometimes a low-fat, high carbohydrate diet (such as fruits, vegetables, bread, noodles) is used in addition to L-carnitine. Any changes in the diet should be made by a dietitian. Dietitians know what are the right foods to eat. Ask your doctor whether your child needs to have any changes in his or her diet.

Things to Remember

Always call your doctor when your baby has any of the following:

- poor appetite
- low energy or too much sleepiness
- vomiting
- diarrhea
- an infection
- a fever
- continued muscle pain or weakness

Babies with CUD need to eat extra starchy food (such as rice, cereal, bread) and drink more fluids when they're sick - even if they don't feel hungry – or they could have a Metabolic Crisis. If they won't or can't eat, they may need to be treated in the hospital to prevent serious health problems.

3-methylcrotonyl-CoA carboxylase deficiency

(3-MCC; 3-methylcrotonylglycinuria;
isolated deficiency of 3-methylcrotonyl-CoA carboxylase)

Technical advisory committee report

Treatment
Clinical variability ranges from serious to benign (there is debate as to the clinical significance of the condition). Similarly, there is not consensus regarding treatment, or the need to treat.

Available Technology – Screen
It appears that screening identifies many infants who would remain asymptomatic without intervention. The screening test is also positive for infants with 3-hydroxy-3-methylglutaric aciduria (HMG) which is also on the recommended panel as well as two conditions that are not on the list: 3-methylglutaconic aciduria (3MGA) and 2-methyl-3-hydroxy butyric aciduria (2M3HBA).

Concordance with Treatment and Screening Technology criteria:
Less concordance

Estimated frequency
1 in 73,000 births

Disorder family: organic acidemia

Primary screening analyte: C5OH (Zytkovicz, Fitzgerald et al. 2001) C5OH is indistinguishable from 2-methyl-3-hydroxybutyrylcanitine by MS/MS analysis

Secondary screening analytes: low C0 (Sweetman and Williams 2001)

Variability in clinical presentation:

"The clinical course of this disorder ranges from severe to apparently clinically benign." (Sweetman and Williams 2001)

Burden if untreated:

"May include episodes of vomiting, acidosis, hypoglycemia, hypotonia and coma" and death from complications. (Sweetman and Williams 2001)

Efficacy of treatment/benefits of early intervention:

Normal development/effective treatment. (Sweetman and Williams 2001)

“Correct treatment of acute episodes prevents disability in almost all cases.” (2005)

Unintended consequences of screening:

3 other disorders have elevated C5OH or 2-methyl-3-hydroxybutyrylcanitine. (Chace, Kalas et al. 2003)

Cases of asymptomatic maternal 3MCC have been detected by elevations of C5OH in the unaffected newborn. (Gibson, Bennett et al. 1998)

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last modified: 9/6/2007

3-Methylcrotonyl CoA Carboxylase Deficiency
(3MCC)

What is 3MCC?

3MCC is a type of organic acid disorder. People with this condition can't break down an amino acid called leucine from the food they eat.

What Causes 3MCC?

Enzymes help start chemical reactions in the body. 3MCC happens when an enzyme called "3-methylcrotonyl CoA carboxylase (3MCC)" is missing or doesn't work right. This enzyme helps break down leucine. All foods with protein contain leucine. Harmful matter can build up in the blood and cause problems when someone with 3MCC eats protein.

What Symptoms or Problems Occur with 3MCC?

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

Symptoms of 3MCC vary. Many people with 3MCC have no symptoms. Others have periods of illness called Metabolic Crises. Some of the first signs are:

- poor appetite
- too much sleepiness or lack of energy
- muscle weakness
- irritable mood
- other behavior changes (such as crying for no reason)
- vomiting

If a Metabolic Crisis is not treated, a child with 3MCC might develop:

- breathing problems
- seizures
- liver failure
- coma, sometimes leading to death

Later problems can include:

- low muscle tone
- weakness
- lack of energy
- poor growth

What is the Treatment for 3MCC?

These treatments are sometimes used for babies and children with 3MCC:

1. **Low-leucine diet** - Most foods in a low-leucine diet will be carbohydrates (such as bread, cereal, noodles, fruits, vegetables). High-protein foods to limit or avoid include:
   - milk and milk products
   - meat and poultry
   - fish
   - eggs
   - dried beans and peas
   - nuts/peanut butter
2. **Medical foods and formula** – There are special medical foods available for people with 3MCC. These foods include special low-protein flours, noodles, and rice. Some children also need a special leucine-free formula. A dietitian will tell you how to use these foods and formula. Dietitians know what are the right foods to eat.
3. **Medications** – The doctor may prescribe L-carnitine for your child. This is safe and natural and helps cells make energy. It also helps the body get rid of harmful wastes.

Things to Remember

Minor illnesses such as a cold or flu can cause a Metabolic Crisis in some children with 3MCC. You may need to call your doctor right away when your child has any of the following:

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

Some children with 3MCC need to eat more starchy foods (such as bread, cereal, rice) and drink more fluids when they are sick - even if they are not hungry – to avoid a Metabolic Crisis.

Tyrosinemia type 1

(Hepatorenal tyrosinemia; Hereditary infantile tyrosinemia; Hereditary tyrosinemia type 1; Fumarylacetoacetate hydrolase (FAH); Fumarylacetoacetase deficiency; Congenital tyrosinosis)

Technical advisory committee report

Treatment
Treatment is very effective at reducing morbidity and mortality.

Available Technology - Screen
Current methodology is very poor for detecting affected infants (poor sensitivity) and results in very many false positives (poor specificity). New methods are being developed that appear to be very effective in initial trials. These may be validated and available for routine use in the near future. Although the new methods also use tandem mass spectrometry (MS/MS), they require a different set-up of the equipment than the other disorders presented here and would probably require acquisition of additional instruments.

Concordance with Treatment and Screening Technology criteria:
Less concordance

Estimated frequency
1 in 120,000 births

Disorder family: amino acidemia

Primary screening analyte: tyrosine (Schulze, Frommhold et al. 2001)

Secondary screening analytes: succinyl acetone, ALA dehydratase (Schulze, Frommhold et al. 2001), tyr/phe ratio (Zytkovicz, Fitzgerald et al. 2001), methionine (CHRMC procedures)

Variability in clinical presentation:

Two clinical forms have been described: an acute form appearing within the first few months of life marked by jaundice and hepatosplenomegaly, and a more chronic form presenting with rickets and hypoglycemia by six months of age. Both present with failure to thrive and a cabbage-like odor (2005)

"In its most severe form, affected infants die from liver failure in the first few months of life" (Allard, Grenier et al. 2004)

Burden if untreated:

Life-threatening progressive liver disease leading to cirrhosis and hepatocellular carcinoma and renal tubular disease (Fanconi syndrome) (Sander, Janzen et al. 2006)

Efficacy of treatment/benefits of early intervention:

Significantly reduces mortality and morbidity (Allard, Grenier et al. 2004)

"Treatment leads to improvements in kidney, liver and neurologic function" (2005)

Unintended consequences of screening:

"Tyrosine measurement in dried blood spot specimens alone lacks specificity as other disorders of tyrosine catabolism and benign hypertyrosinemia of the newborn can lead to increased tyrosine" (Schulze, Frommhold et al. 2001)

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last modified: 8/25/2006

Tyrosinemia
(TYR1)

What is TYR1?

TYR1 is an amino acid disorder. People with TYR1 can't break down the amino acid tyrosine from the food they eat. This causes severe liver disease and other health problems if not treated.

What Causes TYR1?

Enzymes help start chemical reactions in the body. TYR1 happens when the enzyme fumarylacetoacetase (FAH) is missing or not working. When FAH doesn't work, it can't break down tyrosine. Tyrosine and other harmful things then collect in the blood. One of these is succinylacetone. This causes serious liver and kidney damage. It can also cause periods of weakness or pain.

What Symptoms or Problems Occur with TYR1?

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

Babies usually show symptoms in the first few months of life. Some of the first signs are:

- diarrhea and bloody stools
- vomiting
- poor weight gain
- too much sleepiness
- irritable mood
- "cabbage-like" odor to the skin or urine

Liver problems are common. They can cause:

- enlarged liver
- yellow skin
- bleeding and bruising easily
- swollen legs and stomach

Kidney problems also happen and can cause:

- rickets, a bone thinning condition
- delays in walking

Babies with severe liver and kidney problems usually die without quick treatment.

What is the Treatment for TYR1?

Doctors use these treatments for children with TYR1:

1. **Medication** – The doctor may prescribe Nitisinone (Orfadin®). This prevents liver and kidney damage. It also stops the weakness and pain. This medicine may lessen the risk of liver cancer. Your child should take Nitisinone right away.
2. **Medical Formula** – The doctor may prescribe a special formula with the right amount of amino acids. He or she will tell you what kind is best and how much to use.
3. **Low-tyrosine diet:** Most children with TYR1 need to limit foods such as cow's milk and regular formula. Your doctor and dietitian will decide on the best food plan for your child. Dietitians know what are the right formulas and foods to eat.
4. **Blood, urine, and other tests** – Regular blood and urine tests will show if your child's diet or medicine needs to be changed.
5. **Liver transplantation** – A liver transplant is one way to prevent liver cancer.

Things to Remember

Early treatment can prevent severe symptoms of liver and kidney problems and weakness and pain. Children who are treated early usually have normal growth and intelligence.

If treatment isn't started right away, children may have liver or kidney damage. Rickets might be a problem and need treatment. Delays in growth and development can also happen.