Urea cycle disorders

A guide for patients, parents and families

Contents

Introduction

You or your child have/has been diagnosed with a urea cycle disorder.

Initially any information regarding these types of condition is hard to understand, especially at a time when you are naturally very worried and suddenly provided with lots of medical information.

By describing this condition in booklet format, you will be able to read it at your leisure, and then write down any important questions that you may want to ask your specialist doctor, nurse or dietitian.

We're here to help. For more information, resources or family support, contact:

National Urea Cycle Disorders Foundation
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75 S. Grand Ave. | Pasadena, California 91105 | Phone: 626 578-0833

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Metabolic function

To be a fit healthy individual, we have to feed our body regularly with food to provide energy and repair tissues.

The foods that we eat are broken down into small packages and either used for growth and repair, stored to be available for periods of starvation, or disposed of as waste. This explanation describes the basic process, but it is of course much more complex.

How the body deals with protein

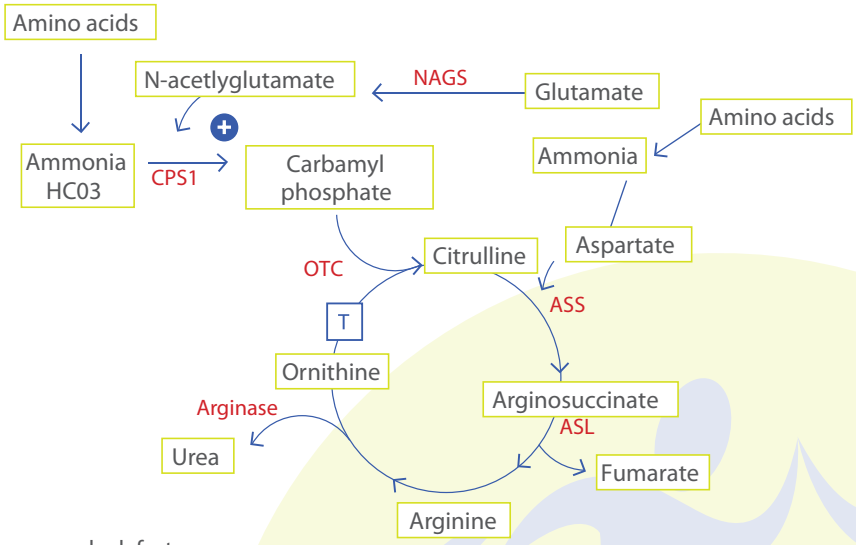
Foods containing protein are eggs, milk, fish, meat, cheese, bread etc. During digestion, protein is broken down into smaller molecules or "building blocks" to be transported in the blood and used for growth and tissue repair.

What started as a healthy steak or a glass of milk will have now been broken down into 20 individual "building blocks" known as amino acids. These amino acids travel in the bloodstream and are supplied to the cells where they are needed. Generally speaking, we consume much more protein than the body needs. Once we have finished with using what is needed, the excess is broken down by enzymes into smaller products, including ammonia and organic acids. The body is unable to tolerate large amounts of ammonia and organic acids; therefore a process in the liver converts these into harmless forms that can then be disposed of. This is where the urea cycle comes in.

The urea cycle

Having explained the basic function of protein metabolism, it is helpful to understand a little about the urea cycle. As previously described, the body needs a way to dispose of the ammonia. This is carried out in the liver, by a continuous process called 'the urea cycle.' As the cycle turns, the toxic ammonia is changed, step by step, into urea (a nontoxic component in the blood), which is later excreted.

The urea cycle is controlled by a series of enzymes. In urea cycle disorders one of these six enzymes is not working correctly, and the cycle is interrupted.



The urea cycle defects are:

- NAGS – N-acetylglutamate synthase deficiency
- CPS1 – Carbamoyl Phosphate synthase deficiency
- OTC – Ornithine transcarbamylase deficiency
- ASS – Citrullinemia or argininosuccinate synthase deficiency
- ASA/ASL – Argininosuccinic aciduria or Argininosuccinate lyase deficiency
- Arginase – Arginase deficiency

What are the symptoms?

Symptoms vary from individual to individual, and may present at any age.

During the first week of life a baby can become very unwell once the baby is fed. This protein intake may exceed the capacity of the urea cycle. Babies with severe UCD may refuse to feed and then present with drowsiness, rapid breathing and vomiting. Hospitalization will be necessary to lower the level of ammonia in the blood and to aid the baby with breathing.

Older children with a urea cycle disorder may become very ill, having had a healthy childhood with no sickness prior to this deterioration. This so-called "decompensation" may be triggered by an illness such as a cold or virus. Sometimes a sudden increase in the amount of protein eaten while on vacation or following a celebration may also precipitate these types of symptoms. When the doctor takes a medical history it is common for parents to recall or comment on fussy eating habits without being aware that their child is self-selecting a diet low in protein. It is usually the onset of acute illness and coma along with the clue in dietary history that will lead to the investigations required to diagnose a urea cycle disorder.

There is also a group of older patients - teenagers and adults, which present with episodes of vomiting, agitation, unusual behavior or drowsiness. They may appear intoxicated. They may require a short stay in the hospital or emergency room and are given extra fluids, often through a drip directly into the vein. It is usually only after more than one admission, that a doctor is likely to become concerned and may diagnose a urea cycle disorder after further investigation.

Treatment

Aims of treatment

The main aim of treatment is to keep the level of ammonia in the blood down at safe levels. Several things may cause the blood ammonia to rise. These include infections or sudden increase in the amount of protein eaten. During periods of illness and infection, the body's response is to break down lean tissue to supply energy. As a result of this, protein is also broken down and released back into the blood stream, which in turn leads to the ammonia level going up.

Emergency treatment during acute illnesses

If your child is feeling unwell, they should be treated with an emergency regime. An emergency regimen is necessary for every patient who has a urea cycle disorder, including those who may be mildly affected. This treatment varies specifically from one individual to the next.

Contact your metabolic physician immediately if your child develops a virus, has a fever, diarrhea or vomiting, or appears unusually lethargic or agitated. By immediately adjusting the diet regimen to prevent production of excessive ammonia, your child may remain stable enough to prevent hospitalization.

The emergency regimen is prescribed to suit your child as an individual, it is regularly revised and the adjusted according to the child's age and weight. It is important that the instructions are followed rigidly during illness and the child is able to tolerate the regimen throughout the day and night.

Your dietitian will advise you on the emergency regimen and provide some written instructions for you.

If while on the emergency regimen, your child continues to vomit and it is apparent that he/she is not recovering, you must either:

- contact your metabolic specialist and arrange for hospital admission,
- or go to the emergency room and contact your metabolic specialist
- or telephone your pediatric unit (if you have an access facility that allows pre-arranged admission).

While in hospital, it will be necessary to take blood tests to ensure that the blood chemistry is becoming normal again. One of the blood tests measures ammonia. During phases of illness, ammonia can easily become raised; therefore it is necessary to check it regularly.

If during hospital admission, your child is not responding well to the dextrose drip, further treatment will be needed. If ammonia is allowed to rise to very high levels, drowsiness, irritability and confusion occurs, warning us that the brain is being affected. In order to prevent this from occurring, it may become necessary to treat with medicines through the vein because your child can't take their regular medications by mouth. The medications used are called sodium phenylbutyrate plus sodium benzoate (Ammonul) or N-carbamylglutamate (described later on in the booklet). Arginine for ASA/ASL and citrullinemia, or citrulline (only for OTC deficiency) are used to help the urea cycle work harder to remove ammonia. If these medications have been introduced and your child continues to remain very sick with high ammonia in the bloodstream, it will be necessary to transfer to a unit where a dialysis machine will be set up for the child. Dialysis works by filtering the patient's own blood through a machine removing the harmful ammonnia and returning the filtered blood to the body.

Long term treatment

Diet

Patients that are diagnosed with a urea cycle disorder often have their dietary protein restricted, or they are advised to be a cautious with the amount of protein they eat.

Restriction of protein is important because it reduces the workload on the urea cycle. The aim is to provide the body with sufficient protein to allow for growth and repair of tissue but at the same time reducing quantities to a level that your child can tolerate. There is a tendency for the amount of protein tolerated to decrease with time because as you get older the growth rate slows.

Your dietitian will teach you how to measure protein so that you will be able to control and measure the amount of protein you are allowed in the diet. The protein allowance is highly personalized. What may be enough for one patient may be way too much for another. Always follow the prescribed amount closely.

Some individuals with UCD develop food aversions because because they often feel nauseous from levels of ammonia in the blood. In this instance use of a tube for feeding becomes essential.

Tube feeds can be given by passing a very fine tube down the nose and into the stomach. These are referred to as naso-gastric tubes. Naso-gastric tubes are not recommended for long term use If it becomes obvious that long term tube feeding will be required, insertion of a gastrostomy tube may become necessary. A gastrostomy tube is inserted directly into the stomach and is per - formed under anaesthetic as a minor surgical procedure. A small plastic disc that sits just under the skin secures the gastrostomy tube. When the child is not connected to a feed, the tube is clamped and clothes are worn over the tube covering the site.

Liver transplantation

Liver transplantation has been increasingly used in urea cycle disorders in neonatal-onset disorders (the most severe) or when optimal management fails to control the disorder. Liver transplant is considered a cure, however, patients still require the use of arginine or citrulline in addition to the immunosuppressant medications necessary in organ transplant.

Medication

Part of the long-term treatment to keep the ammonia levels down involves the use of a range of different medicines. The medicines are used in different combinations and are specific to the individual patient

ARGININE: this is an essential amino acid located in the urea cycle use in ASA and AS. Arginine is not used in arginase deficiency. Taking extra arginine as a medication will help the urea cycle work more efficiently.

CARGLUMIC ACID: is also known as N-CARBAMYLGLUTAMATE: this is a medicine of choice in N-acetylglutamate deficiency (NAGS deficiency) to re-activate the urea cycle. It may also be used when a as part of the clinical trial for CPS1.
or therapy trial.

CITRULLINE: is substituted for arginine in CPS1 and OTC patients. It is not used in citrullinemia, ASA, or arginase deficiency.

SODIUM BENZOATE: this medicine also reduces the amount of ammonia in a similar way to sodium phenylbutyrate, but through a different pathway.

SODIUM PHENYLBUTYRATE: this medicine is used to reduce the amount of ammonia in the blood.

It is very important that you take all your medication as prescribed by your doctor.

How did my child get this condition?

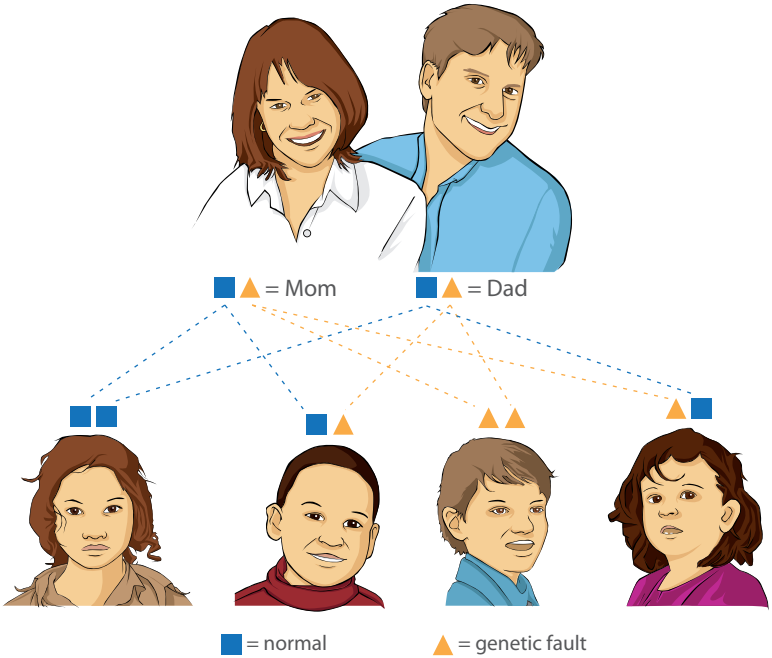
Urea cycle disorders are usually genetic. This means that they are not brought about by anything that may have occurred during pregnancy. Genetic disorders are inherited and the pattern in which your child may have developed the condition will now be described.

If the gene is inherited from both mom and dad it is described as autosomal recessive. OTC deficiency is X-linked (described on page13).

In the human body, every person carries approximately seven defects in their genetic information. If you and your partner both carry the same genetic fault, there is a chance that your baby will be inherit that genetic fault. The risk of inheritance for UCD depends on the disorder involved.

How does this occur?

The diagram shows you how this happens.



Unaffected child. Not a carrier.
Unaffected child. Carries the genetic fault.
Child that has the condition.
Unaffected child. Carries the genetic fault.

When a child is conceived, there is no way of predicting which sperm and which egg will unite to make the baby. At conception one egg from mom and one sperm from dad is brought together to create the fetus.

It is within the nucleus of each cell of the egg and the sperm that information called "DNA" is stored on strands called chromosomes. It is this information that predicts the colour of the child's eyes, hair, etc. and will also carry any information that relates to a genetic disease.

X – Linked disease

A person's gender or sex is determined by the so-called sex chromosomes. They exist in two types, X-chromosomes and Y-chromosomes. A female has 2 X-chromosomes and a male has 1 X and 1 Y.

One of the more common urea cycle disorders is called OTC, this stands for ornithine transcarbamoylase deficiency. It is inherited as an X linked disease. This means that this type of disorder is passed on from parents to baby through the X chromosome. If the baby is a female, because females have two X-chromosomes, the good X can balance out the problem with the faulty X. But because males only have one X chromosome, it can't be balanced by a normal X as in the female, and as a result in males, this disease tends to be more severe. Occasionally, a child may develop a urea cycle disorder that is not inherited. In such cases, the risk of any future children developing the disorder is extremely small. It is important with all urea cycle disorders, that a geneticist is involved, to establish whether or not the condition has evolved independently or has been inherited.

You will be offered the opportunity to meet with a geneticist to discuss your child's condition.

What does the future hold for my child?

As previously described, the severity of urea cycle diseases is very variable. In some cases, the condition is so mild that the specialist needs only to see the child on an annual basis. With this group of patients an annual check up allows the doctor to keep up to date with any changes that may be occurring as the patient gets older. With increasing age it may become necessary to reduce protein intake and start medication.

For those children that are more severely affected, it is important to be seen and assessed regularly by a metabolic team. It is likely that the more severely affected child will need the support of specialists and access to interventional therapies in addition to the metabolic doctor. This specialists may include include neurologists, special needs social workers, speech therapy, physiotherapy, as well as your pediatrician, paediatric nurse etc.

Children that are severely affected may have learning difficulties and may therefore need assessing to ensure the education he/she receives is suitable to the child's learning ability.

Pregnancy

While urea cycle disorders are regarded as fairly serious diseases, treatments are constantly being refined, and ongoing research means that the long term outcome for patients is improving. Of course, this will always depend on the type and severity of the urea cycle disorder which the individual person has.

Having a baby as a fit and healthy individual imposes a significant amount of stress and fatigue on the body. As a patient with a urea cycle disorder, the effect of a pregnancy will increase this stress level and can cause problems to both mother and child if not cared for appropriately.

It is advised that all females involved in sexual relationships receive family planning counseling. Where possible all pregnancies should be carefully planned and care provided pre-conceptually with your Metabolic Specialist.

During your pregnancy. your care will be coordinated between your metabolic specialist and your obstetrics team. This ensures that throughout pregnancy both mother and baby are provided with the maximum support available. It is likely that you will be monitored more closely and some of the treatment, maybe the diet or medication, will be changed.

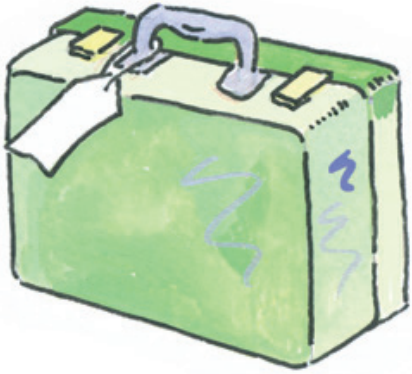
Traveling

Traveling is sometimes a part of everyday life, and careful preparation is necessary for individuals with UCD. It is wise to take sensible precautions if planning an extended trip or if going abroad.

It is necessary to check to make sure that your destination has suitable medical facilities locally should the individual with UCD become ill while away from home.

It is absolutely necessary to continue with your diet and medi cation while away and to ensure that you have adequate supplies to last you for your trip.

You should carry information regarding the nature of the disorder and this can be provided by your clinical team. There are some UCD emergency cards produced for this purpose that contain specific information about UCD and and its treatment. For longer periods abroad your medical team may be able to refer you to a local metabolic specialist that could supervise your care.



Glossary

Acute: sudden onset, severe

Amino acids: the building blocks of proteins

Ammonia: toxic by-product of the breakdown of protein in the body

Chronic: long-term

Decompensation: a metabolic term describing onset of illness resulting in thebody reverting to the breakdown of stored protein within the cells and tissue. Usually it is brought about by diarrhoea and vomiting or mild infection.

Elimination: the way in which the body gets rid of waste materials in urine or feces

Enzyme: a chemical in the body that makes the chemical reactions proceed more quickly

Gastrostomy: a feeding tube which is placed directly through the stomach wall

Intravenous: into the blood vein

Naso- gastric tube: a feeding tube which goes via the nose into the stomach

Orally: by mouth

Pediatrician: a doctor who trains specifically in the care of children

Urea: ammonia is converted into urea it is less toxic and can be passed in the urine.