Information on CTD
(Carnitine Transporter Deficiency)

This fact sheet provides information for individuals with CTD, their family and friends, and other interested groups.

We hope that this fact sheet will provide some insight into the latest information on CTD. We are, however aware that this condition presents in a variety of ways and that continued scientific research will provide greater understanding about the nature of this genetic condition in the future.

The intent is to make any new information available on the website, www.hmr.fo, which is the official website of the Ministry of Health. The information on the website will be updated as new knowledge is obtained or as changes occur in the practical management of the disorder.

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WHAT IS CTD?

CTD stands for “Carnitine Transporter Deficiency or Defect”. Those with CTD have difficulty producing energy from fat (also called beta-oxidation of fatty acids), which is one of the most important sources of energy for the body.

The normal oxidation of fat or fat “burning” is dependent on a high level of carnitine in the cells of the body. Carnitine normally is available in the food (meat contains an especially large quantity of carnitine). Carnitine is also produced by the body itself.

To ensure that there is enough carnitine in the cells, the body produces a special protein called a carnitine transporter that “transports” carnitine through the cell membrane. Further the transporter reabsorb carnitine that was filtered into urine back into blood. This transporter “pump” does not work well in people with CTD. Thus carnitine is lost in urine and level of carnitine in cells gets too low to allow an optimal oxidation or burning of fat in the cells. This can result in a lack of energy and in some cases to a complete blockage of fat oxidation, as well as other disruptions in cell function.

Generally, people with CTD who eat and drink normally can produce sufficient energy from the processing of sugar, other carbohydrates and protein. However, a person with CTD who fasts or vomits repeatedly, may develop symptoms such as

drowsiness because the cells cannot easily shift their energy production to the burning of fat, as normally would be the case. This means that the organs that use the most energy have difficulties getting the energy they need. These organs include the brain and the muscles, especially the heart.

Medical research has shown that children with CTD quickly develop a life-threatening energy deficiency in connection with infectious diseases that are accompanied by recurrent vomiting and / or high fever. In these situations, it is extremely important that children quickly receive carnitine and sugar directly into the blood (intravenously) until they are again well and can eat and drink normally.

CTD can also slowly affect the heart over time. Eventually, the heart muscle can enlarge. The cells in the heart that conduct the electrical impulses causing the heart to beat might get harmed. This can lead to sudden death caused by irregular heartbeat.

WHY DO SOME PEOPLE HAVE CTD?

CTD is an inherited genetic disorder. To have the disorder, one must inherit two mutated genes (one from each parent).

The incidence of the disorder in most countries is very low (1:100,000), but in the Faroes the disorder is relatively common. Based on the current number of known cases, it is estimated that more than 1 in every 400 Faroese has CTD.

The reason is the relative isolation of the Faroese population through centuries and it is not unusual that a couple has close common ancestors and thus both parents could bear the same (abnormal) defective CTD gene.

Even though CTD has always been present in the Faroes, it was not until 1995 that physicians diagnosed the first case of the disorder. It has only been within the last ten years, however, that we have come to learn how widespread and serious the disorder is in the Faroes.

SYMPTOMS OF CTD

Because CTD is so uncommon around the world and has only recently been described, there is much about the disorder that is unknown and much more research is needed. Some children with CTD have presented with slow growth, complications following infections, and diminished muscle tone. In other cases the disorder is without symptoms.

In the Faroes, it has been well established that CTD can be serious in two ways:

1) If babies with CTD get infections, especially when associated with vomiting, many of them become lethargic and subsequently fall unconscious from low blood sugar. If treatment with carnitine and sugar is not initiated immediately, the child could die or develop severe brain damage.

2) In others with CTD, the disorder initially can be without obvious consequences, But later CTD can cause problems for the heart, which in certain cases can lead to sudden death.

HOW DO YOU FIND OUT WHETHER YOU HAVE CTD?

There are three different ways:

1) Measure carnitine levels in blood. Optimally, we want to measure the level of carnitine in cells, but as this is technically difficult, researchers instead use the carnitine levels in blood assuming some degree of correlation with carntine levels in cells. There are several procedures to determine blood carnitine levels, and therefore "normal" levels differ. Thus, in order to accurately interpret specific values, one must know the "normal" values for the specific test used (see the suggested values listed under FAQ).

2) Genetic screening. In the Faroes, CTD often is caused by a genetic variant in the transporter gene called N32S, but there are five other known genetic variants in the Faroes. Four are well studied and can be detected by genetic screening. For the risk of overlooking a CTD case with one or two copies of the unknown mutation genetic screening is currently not used.

3) Measure the activity of carnitine transporters in cultured skin cells. This particular method takes a long time and is very expensive and is only recommended in the rare case in which a diagnosis of CTD is strongly suspected, but there is no other way to definitively confirm the diagnose of CTD.

TREATMENT

Treatment is simple and consists of giving the patient sufficiently large doses of carnitine so that the level of carnitine in the blood remains close to the lowest "normal" value for blood levels of carnitine. In this way, sufficient carnitine is transported (inactively) into the cells so that fat oxidation can occur normally.

If children with CTD take carnitine regularly, they will develop normally and are not in greater danger of becoming sick than other children.

It is important to remember that carnitine is quickly filtered out of the body. Therefore, if an individual with CTD begins to repeatedly throw up or otherwise stops taking carnitine, in a very short time there will be a shortage of carnitine in the body. In such situations, it may be necessary to go to the hospital for intravenous carnitine treatment.

Certain types of medicine lead to a carnitine depletion and therefore should not be given to people with CTD. This is especially true for antibiotics containing pivalic acid (like Pondicillin® and Selexid®) and valproate or valproic acid (used in the treatment of epilepsy).

Those with CTD can increase their carnitine uptake to a certain extent by eating often and by eating food that naturally contains carnitine. For example, red meat has very high levels of carnitine, but eating meat alone can never replace regular carnitine treatment and should not be considered as a primary treatment for CTD.

PREVENTION

Since 17 March 2003, all newborn children in the Faroes are offered a so-called "extended screening" that includes a screening for CTD. In the beginning, the screening was provided only to those parents who said "yes" to the screening. However, from 25 January 2009, all newborns in the Faroes are screened for CTD.

The screening for CTD is very effective. However, because it is a screening-test, it will not be 100% reliable and in addition some types of antibiotics can impact the result. Thus, if symptoms arise that are consistent with CTD, it is important to ask for the test to be redone or to have your family doctor perform other tests to determine the presence of CTD.

QUESTIONS AND ANSWERS ON CTD/FAQs

My child was born between 17 March 2003 and 24 January 2009. Can I find out if my child was screened for CTD?

Answer: If you remember being asked if you wanted an extended PKU test, you can be assured that the test was conducted and, if you did not hear anything, that everything was as it should be. If you do not remember being asked, the result can be obtained from the Screening Department of the National Hospital. You can get the result by sending an email to screeningseindin@ls.fo, or by calling 304500, extension 5619 or 5600. Please provide the name and birth date of the newborn and the name and birthday of the mother.

Can a carrier of a mutation in the transporter gene manifest symptoms of CTD?
Answer: CTD-carriers have diminished functioning of the carnitine transport mechanism at about half of normal function, and their blood levels of carnitine are lower than those of non-carriers. However, at no time has this been shown to have any clinical consequences. CTD-carriers, for example, have never suffered from any severe diseases or death that could be linked to CTD. Researchers are interested to see if carriers experience any increased risk of heart disease or any increased tendency to miscarry, but to date no linkage has been shown. It is planned to conduct further scientific investigations to clarify this ongoing concern.

Should carriers be treated with carnitine?
Answer: To date, no studies have demonstrated the efficacy of providing extra carnitine to CTD-carriers. Thus, it is not recommended to give carnitine to CTD-carriers.

Should pregnant CTD-carriers be treated with carnitine?
Answer: No, even though it is well-known that CTD-carriers who are pregnant have lower blood carnitine levels than those who are not pregnant, there is no evidence that this has any consequences for neither the mother nor the foetus.

In general is it not recommended to test for CTD during pregnancy. However if a woman is pregnant when testing for CTD it is recommended that she is tested again 6 months after giving birth. One can consider if pregnant women from families with a child affected with CTD should be treated with carnitine supplement – not for the mother but in order to give a potential affected foetus the best conditions.
Can one have low blood carnitine levels from diseases other than CTD?

Answer: Yes, and two of these disorders are also relatively common in the Faroes. One is known as HCS deficiency and requires treatment with the vitamin biotin. The other disorder is called 3-MCC deficiency and was treated previously with carnitine, but today it is believed unnecessary to provide supplements of carnitine unless symptoms of the disorder are present.

Is it possible to get a genetic screening for CTD?
Answer: Yes, but with the caveat that not all of the gene variants related to CTD are known. Therefore, genetic screening for CTD is not recommended, as only known gene variants will be found.

What is the normal blood carnitine level?
Answer: This is a difficult question as there are several different laboratories which conduct such tests. They have each their own procedures and their own normal values for blood carnitine. The Table below shows the different values for each of the laboratories used in Faroes patients:

	Normal	Possible CTD carrier	Evidence of possible CTD disorder
Free plasma carnitine measured by Metabolic Laboratory, Copenhagen University Hospital (Rigshospitalet)	24-64 µmol/l	10-24 µmol/l	<10 µmol/l
Free carnitine (derivatised) in dry blood, Hannover, Germany	>28 µmol/l	<28 µmol/l	
Free carnitine (underivatised) in dry blood Hannover, Germany	>12 µmol/l	5-12 µmol/l	<5 µmol/l

µmol/l = micro mole per litre, a scientific way to state the quantity of carnitine in the blood.

How can I be screened for CTD?
Answer: If you were born before 1985 and your parents are closely related to a person who had CTD, ask your doctor and request a free blood test for you to determine the level of free carnitine in your dried blood. In this connection, "closely related" means parents, siblings, cousins or second cousins related to one person who has CTD.

All other Faroese can get the same screening for a fee of 100 DKK, which is to be paid at the time blood is drawn for the test. For more information, see www.hmr.fo.

The level of blood carnitine in all Faroese born after 1985 have been determined by testing the blood drawn at birth from each newborn for the so-called "PKU test". These blood samples are stored at the Seruminstituttet and have been tested.

As for newborn screening, both test-situation will not give 100% reliable test-results. Therefore, those who present with symptoms consistent with CTD should have their blood retested.

Is it necessary to fast before they draw my blood to measure my levels of carnitine?
Answer: No, it is not necessary to fast before the blood test.

Will I get the results of my screening?
Answer: No, only the individuals who have low values will be personally contacted by the responsible clinician at the National Hospital to arrange for further tests that will determine if the person has CTD or not. Carnitine treatment will be started and continued until the final results of the tests are available.

How can I be screened if I am Faroese and live outside the Faroes?
Answer: If you were born before 1985 and both of your parents are Faroese, you should go to your local doctor in the area where you reside and ask to have your blood tested for free carnitine. Guidelines regarding this have been prepared by the Danish National Board of Health and can be found on http://www.sst.dk/Nyhedscenter/Nyheder/2010/CTD_Screening.aspx . If you are Faroese and born between 1985 and 16 March 2003 and your mother has a Faroese social security number, your level of carnitine at birth have been determined by testing the blood drawn at birth from each newborn for the so-called "PKU test" (see above).