Ornithine transcarbamylase (OTC) deficiency is classified as a urea cycle disorder. The urea cycle is a process in which the body removes ammonia (a waste product from the breakdown of proteins) from the body. This process most commonly occurs in the liver. People with a urea cycle disorder have difficulties breaking down and getting rid of ammonia, which can cause an accumulation of ammonia in the body that can be toxic, particularly to the neurological system.

This toxicity to the body is what will cause the symptoms seen in OTC deficiency. Symptoms can begin as early as the newborn period, or as late as adulthood. Some of the health issues that OTC deficiency can lead to include periods of vomiting, lethargy, tachypnea (hyperventilation), failure to thrive, or acute fatty liver. Between episodes they can have anorexia, nausea, and protein intolerance. Other complications of OTC deficiency may include seizures, behavioral problems, developmental delays, cognitive impairment, and other types of neurological concerns. In some cases, if not recognized early or left untreated, OTC deficiency can lead to coma and even death.

Causes

We have over 20,000 different genes in the body. These genes are like instruction manuals for how to build a protein, and each protein has an important function that helps to keep our body working how it should. The *OTC* gene makes a protein called ornithine transcarbamylase (OTC). The OTC protein is active in helping with urea cycle in the liver to prevent ammonia from building up, which can be toxic to the nervous system. If someone has a harmful change (called a pathogenic variant) in their *OTC* gene, then their body is not going to make as much OTC protein as it should. If the body does not have enough OTC protein, then the urea cycle cannot work like it should, which leads to a toxic buildup of ammonia in the body. This is what leads to the signs and symptoms we associate with OTC deficiency.

The *OTC* gene is located on the X chromosome, so OTC deficiency is inherited in an X-linked pattern. Males only have one copy of their X chromosome, and therefore only one copy of all the genes that are on the X chromosome. Females have two X chromosomes, so they have two copies of all the genes on the X chromosome. This means that males with OTC deficiency will produce little to no OTC protein, while females may produce some due to their second working copy of the gene. Because of this difference, males are often more severely affected and will often develop health issues at younger ages in comparison to females.

It is estimated that approximately 1 in 14,000 to 1 in 77,000 people have OTC deficiency. It

may be more common because some people may have mild symptoms and not show any symptoms until much later in life.

Genetic Testing for OTC deficiency

Genetic testing for pathogenic variants in *OTC* is available. There are several different ways to approach to testing depending on the medical and family history, and any prior testing that may have been done. Different approaches include:

- *Single site analysis*: Testing specific to a known pathogenic variant in the family
- *Full gene sequencing and rearrangement analysis*: Comprehensive testing to search for all currently detectable pathogenic variants in the *OTC* gene.
- *Gene panels*: Newer, more broadly based gene tests that would include not only the *OTC* gene, but other genes known or suspected to be associated with the patient's medical concerns

Diagnosing OTC deficiency

The diagnosis of OTC deficiency is often made following an episode or medical history that is concerning for OTC deficiency, or due to a positive family history. OTC deficiency is often diagnosed through measurements of levels in the blood and urine in combination with either genetic testing or measurement of enzyme activity in the skin or liver (both would require a biopsy to be done). OTC deficiency is also detected through newborn screening in some states.

Medical Management for OTC deficiency

Management of OTC deficiency is focused on preventing episodes of high ammonia levels (which can lead to a crisis and the symptoms described above). Affected individuals may require a protein-restricted diet, the use of nitrogen scavengers (medications that help remove ammonia), and other medical supplements. Some people with OTC deficiency may eventually require a liver transplant if the condition becomes difficult to manage. This is particularly true for those who start showing symptoms in the newborn period.

Precautions are also taken to help reduce the risk for an episode. This includes avoiding fasting, stress, and specific medications. For females, additional precautions may be put in place during pregnancy and delivery, due to the stress this can put on the body.

Click here to learn more about scheduling a genetic counseling appointment for pregnancy-related questions.

Click here to learn more about scheduling a genetic counseling appointment for infertility or preconception questions.

Click here to learn more about scheduling a genetic counseling appointment for questions about pediatric or adult genetic conditions.

Additional Resources

National Urea Cycle Disorders Foundation