

What is Guanosine Triphosphate Cyclohydrolase I Deficiency (GCH I, GTP Cyclohydrolase, GTPCH)?

Guanosine Triphosphate Cyclohydrolase I Deficiency (GTPCH) deficiency is a rare metabolic disorder which produces a lack of the cofactor tetrahydrobiopterin (BH4) which is involved in changing the amino acid phenylalanine to tyrosine and then to dopamine, as well as tryptophan to serotonin. GTPCH levels help control the final production of dopamine as well as of other neurotransmitters. GTPCH is critical for normal dopamine and serotonin production. Lack of this cofactor means neurotransmitters are not formed normally and the neurotransmitters dopamine, norepinephrine, epinephrine and serotonin are deficient in the central nervous system and periphery.

Currently there are two forms of GTPCH -1 Deficiency. The first and more common is the autosomal dominant form, also known as Segawa Disease. This form typically responds well to dopamine replacement therapy.

The second form is not as common and is an autosomal recessive form which does not respond as well to treatment for currently unknown reasons.

Depending on the specific form, patients with GTPCH Deficiency can develop movement disorders, autonomic symptoms (blood pressure instability, temperature irregularities), abnormal eye movements and neurological impairment.

What symptoms are associated with GTPCH Deficiency?

A wide range of symptoms can be associated with GTPCH Deficiency, and involvement can vary from mild, moderate to severe. This disorder is typically associated with diurnal fluctuation, meaning the symptoms worsen as the day progresses.

Mild: In the mildest cases often the dominant form of GTPCH walking or running may be clumsy but little else may be noticed initially. Onset often begins with a postural dystonia (abnormal positioning) of one extremity (often the leg) which typically occurs around 6 years of age. Postural tremor (a rhythmic, involuntary muscular contraction which occurs during a fixed arm position or posture) is also common. Symptoms may progress slowly as the child gets older. Children with mild symptoms are often treated successfully with medication.

Moderate: In moderately affected cases, the child may not be able to walk at all, or walking may be extremely difficult. Abnormal eye movements, postural tremor and speech delay may be present. Children with moderate symptoms often respond well to treatment but full benefit of treatment may take many months.

Severe: In the most severe cases children are physically disabled and affected from early infancy. This may be considered to be the recessive form of the disorder, and may be detected through newborn screening for phenylketonuria. Patients may demonstrate all or some of the following symptoms;

Muscle tightness (rigidity, spasticity)
Abnormal posturing (arching of the back)
Tremor
Poor muscle control
Abnormal eye movements (eye deviation upward, downward or towards the nose)
Strabismus (cross-eyed)
Ptosis (droopiness of the eyelids)
Speech delay
Difficulties feeding or swallowing
Constipation
Torticollis (involuntary deviation of the head and neck to one side)
Intermittent color changes
Unexplained low body temperatures or fevers
Low blood sugar
Difficulty regulating blood pressure
EEG abnormal brain wave spiking (misfiring)
Seizures

Children who are severely affected are more difficult to treat, and several medications may be needed. They are unusually vulnerable to side effects of the medications, which can result in excessive movements and irritability. Response may be slow, with some continued benefit over months to years, but may not result in the complete resolution of all symptoms. Symptoms may present or worsen during other childhood viral illnesses.

Children with GTPCH Deficiency are often considered clumsy or uncoordinated and are often initially diagnosed with cerebral palsy, or hereditary spastic paraplegia.

What causes GTPCH Deficiency?

GTPCH can be inherited dominantly, recessively or rarely as a compound heterozygote (falling somewhere between the two previous phenotypes). When inherited as an autosomal recessive trait, GTPCH Deficiency does not occur unless an individual inherits the same defective gene for the same trait from each parent. A child who receives one normal gene and one gene for the disease may be a carrier and possibly not show symptoms, or may be affected with the less severe dominant form of GTPCH. The risk of transmitting the recessive form of the disease to the children of a couple, both of whom are carriers for a recessive disorder is 25%. The risk is the same for each and every pregnancy.

Who gets GTPCH Deficiency?

Studies to date indicate GTPCH deficiency is more common in females. The method of inheritance can impact the type and severity of the disorder. It is suspected that many cases either go unrecognized or misdiagnosed.

How is GTPCH Deficiency diagnosed?

A diagnosis of GTPCH Deficiency is based upon a three stage testing procedure:

STAGE 1

A lumbar puncture (spinal tap) to determine abnormalities of neurotransmitter metabolites.

Note: Testing for PND's is not a routine procedure and requires following specific guidelines. Should the treating physician or consultant require more information on laboratories please refer to the Pediatric Neurotransmitter Disease Association at www.pndassoc.org or contact Keith Hyland PhD, Horizon Molecular Medicine, Atlanta, GA, 678-225-0222, Khyland@horizonmedicine.com

The results of Stage 1 testing will determine whether Stage 2 and/or Stage 3 are appropriate.

STAGE 2

Phenylalanine loading profile with and without tetrahydrobiopterin can be useful to establish the diagnosis and cause of the deficiency. This is done by ingesting a large amount of phenylalanine and having blood drawn to be analyzed at set intervals (similar to a glucose tolerance testing for diabetes). This test will indicate whether there is hyperphenylalaninemia or not.

STAGE 3

Once the diagnosis is suspected on the basis of cerebrospinal fluid studies, the diagnosis should be confirmed by analysis of the GTPCH gene itself. Specific plasma or fibroblast enzymatic assays, and molecular studies may be beneficial if Stage 1 and 2 testing have not been helpful.. This is done via a skin fibroblast sample and results can take some time to come in. There are again specific guidelines for skin sampling and shipping and adherence is critical to the accurate diagnosis of GTPCH Deficiency. For information on how to collect plasma or skin fibroblasts and where to send the samples, or to receive a testing packet, please refer to the above information from Dr. Hyland's laboratory.

Note: If abnormalities of neurotransmitter metabolites are displayed in the Stage 1 testing procedure but are not conclusive and definite for GTPCH Deficiency, then consideration should be given to other Pediatric Neurotransmitter Diseases.

How is GTPCH Deficiency treated?

Presently, the most well established treatment of GTPCH Deficiency is medication to help restore normal dopamine levels. Dopamine itself cannot cross the blood-brain barrier directly and so it is necessary to treat with a compound called L-Dopa in combination with another medication called carbidopa. Sinemet is a commercially available medication which contains both carbidopa and L-dopa together in a single tablet. However, Sinemet was designed to treat adults with Parkinson's disease and the available dosages are much too high in L-Dopa for many infants and young children with GTPCH Deficiency. It is imperative that the pharmacist compound special low doses of L-dopa and carbidopa for children. Children with GTPCH Deficiency can experience excessive movement or irritability with low doses of L-dopa, and extreme irritability, sleeplessness, and vomiting or persistent abnormal movements with excessive doses.

It is important to work closely with the physician to maximize the results of medications and reduce side effects.

For children who are severely affected at less than one year of age, or prove intolerant of low dose L-dopa therapy, additional medications may be beneficial. They include:

Anticholinergic Agents - Artane

Serotonergic Medications

Gastrointestinal Medications

Miscellaneous category

Physical and occupational therapy is recommended. Speech therapy has also been effective in some children

Medical advancements made in gene therapy or stem cell transplantation may someday provide an avenue to cure the disorder.

Selected References

For a complete list of articles on GTPCH Deficiency, please refer to the *Online Mendelian Inheritance in Man* (OMIM) which is linked below. Before clicking, you will need to enter the following information at the OMIM site:

Guanosine Triphosphate Cyclohydrolase I Deficiency

Key Words: "GTP Cyclohydrolase"

Access Listing: 600225

<http://www.ncbi.nlm.nih.gov/omim>

Or for a complete list of up to date references contact the PND Association.