

A Guide to Tyrosine Hydroxylase (TH) Deficiency, or recessive Dopa-responsive Dystonia

What is TH Deficiency?

Tyrosine hydroxylase (TH) deficiency is a rare metabolic disorder characterized by lack of the enzyme involved in converting the amino acid tyrosine to L-dopa. L-dopa is an important chemical in producing dopamine in the brain. Dopamine is the major neurotransmitter which facilitates motor control and movement. A neurotransmitter is an important chemical messenger that helps nerve cells to communicate properly to each other. TH is a critical enzyme in normal dopamine production, and when it is not working properly to produce enough dopamine, major neurologic abnormalities can occur. In addition, dopamine is also important in making two other important neurotransmitters in the brain and body, norepinephrine (noradrenaline) and epinephrine (adrenaline). When dopamine is critically low, these neurotransmitters may be low too. They play important roles in the brain in regulating attention, and they help to maintain normal blood pressure, body temperature and blood sugar levels.

What symptoms are associated with TH deficiency?

A wide range of symptoms can be associated with TH deficiency, associated with mild, moderate and severe phenotypes.

Mild: In the mildest cases, walking or running may be clumsy but little else may be noticed, at least initially. These symptoms may progress slowly as the child gets older, and may not initially be apparent. Sometimes, one side of the body may seem weaker, or the child may begin to walk up on their tiptoes due to some tightness of the leg muscles. Sometimes these children are diagnosed with cerebral palsy; other times they are simply considered clumsy or uncoordinated. Sometimes these children demonstrate some attentional difficulties in school. Essentially all children with mild symptoms are readily treated with medication.

Moderate: In moderately affected cases, the child may not be able to walk at all, or walking may be extremely difficult. Many children demonstrate unusual arm posturing or positions of their arms with attempts to walk or walk on their toes. Speech delay may be present. Many of these children are diagnosed with cerebral palsy of unknown cause. Some of these children may have involuntary eye movements problems. The majority of these children have an excellent response to treatment, but full benefit may take many months.

Severe: In the most severe cases, children are severely disabled and affected from early infancy. This is sometimes known as the infantile Parkinson's disease variant. Infants may demonstrate muscle tightness and rigidity, arching, tremor and poor muscle control, abnormal eye movements which may include involuntary eye deviation upward, downward or towards the nose. They may be diagnosed with intermittent strabismus (cross-eyed). They may have ptosis, or droopiness of the eyelids. They may have speech

delay, or difficulties feeding, chewing or swallowing. Constipation is common. While most children tend toward increased muscle tone (in the legs especially), there are children who have generalized low muscle tone, with poor head control and inability to sit unsupported. They may have torticollis, or involuntary deviation of the head and neck. They may have difficulty directing their hands to a toy, generating a flinging hand motion. Occasional children have been found to suffer from intermittent color changes, unexplained low body temperature or fevers, low blood sugar, and difficulty regulating blood pressure. These symptoms are more likely to occur during another illness the child may be experiencing. Children in the more severely affected group of patients are more difficult to treat, and several medications may be needed to treat symptoms. They are unusually vulnerable to side effects of the medications, which can result in excessive movement 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.

What causes TH deficiency?

TH deficiency is inherited as an autosomal recessive disorder. In recessive disorders, the condition does not occur unless an individual inherits a defective gene copy from each parent. A child who receives only one copy of the defective gene and one normal copy will be a carrier, but will not usually show symptoms. If both parents are carriers for a recessive disorder, the risk of transmitting the disorder to their child is 25%. The risk is the same for each pregnancy. Most affected siblings to date have manifested a similar range of severity, but this may not always necessarily be the case.

Who gets TH deficiency?

It is unclear at present whether males or females are affected any differently. Only a few dozen cases have been identified to date worldwide as of 2003, but we suspect that many cases go unrecognized or misdiagnosed.

How is TH deficiency diagnosed?

At present, the only reliable and readily available way to diagnose TH deficiency is by analyzing the cerebrospinal fluid for neurotransmitter metabolites. This means your doctor will need to perform a spinal tap to obtain this fluid for analysis. It has to be carefully handled and placed on ice immediately or the results will not be valid. Therefore, it is important to find a doctor who is comfortable in performing this procedure.

Once the diagnosis is suspected on the basis of cerebrospinal fluid studies, the diagnosis should be confirmed by analysis of the TH gene itself. This is because the study of the spinal fluid may lead one to strongly suspect the diagnosis, but there are other reasons why the spinal fluid dopamine metabolite levels could be low, including neurodegenerative disorders which lead to a loss of the cells in the brain that produce dopamine. Therefore, if your children has atypical clinical symptoms including seizures,

or fails to respond as expected to treatment, other disorders need to be considered. Your doctor will work with you in helping to sort out these issues.

How is TH deficiency treated?

The most well-established treatment for TH deficiency is to provide L-dopa 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. L-dopa must be combined with another medication, carbidopa, in order for it to get into the brain properly. There is a commercially available medication called Sinemet which contains both carbidopa and L-dopa together in a single tablet. However, this preparation was designed to treat adults with Parkinson's disease, and the dosage is much too high for many infants and young children with TH deficiency. Therefore, we often ask a pharmacist to order and compound special doses of L-dopa and carbidopa for our patients with this disorder. In general, it is advisable to start with no more than 5 to 10 mg L-dopa, combined with at least 15 to 25 mg carbidopa per dose depending on the size, age and severity of symptoms in the affected child. For some reason, the recessive form of dopa-responsive dystonia is very different from the dominantly inherited form in that children are much more likely to get excessive movement or irritability from low doses of L-dopa. Excessive starting doses of L-dopa can result in extreme irritability, sleeplessness or excessive sleepiness, vomiting or sudden intermittent or sustained jerking and twitching movements which can persist for several hours following a single dose.

In children who are severely affected, less than one year of age, or prove intolerant of low dose L-dopa therapy, we typically recommend initial use of an anticholinergic agent such as trihexyphenidyl (Artane) to help reduce excessive muscle spasticity or rigidity. Anticholinergic agents can work in conjunction with dopaminergic agents to smooth out movements and reduce tremor. Adjunctive agents also include selegeline (Eldepryl), which is a monoamine oxidase B inhibitor which helps slow down the breakdown of dopamine in the body. Selegeline can greatly extend the timespan associated with L-dopa treatment, but can result in excessive movements; nausea, vomiting or reflux, or sleep disorder. It should generally be used only early in the day. There are other agents that your doctor may consider with similar mechanisms of action, and may be appropriate in the treatment of your particular child. It is important to remember that these agents all work together, and the presence of side effects doesn't necessarily indicate that a particular medication is bad, just that it or others need to be adjusted appropriately for your child's needs.

Physical and occupational therapy can be very helpful, particularly during the period of institution of medication to help your child adjust to the medications. Speech therapy is also indicated in some children.

For more information, or if you or a family member are interested in participating in an informational database or in research studies on TH deficiency, please contact:

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Investigational Studies

Kathryn J. Swoboda, M.D. is a neurologist and geneticist working closely with the PND association to establish a clinical database of patients and families with TH deficiency to help us better understand this disorder.