



*“Hope for tomorrow  
begins today”*

For more information about Pediatric  
Neurotransmitter Diseases contact us at:

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[www.pndassoc.org](http://www.pndassoc.org)

# A Guide To Tyrosine Hydroxylase Deficiency



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## Mission Statement:

The PND Association is a non-profit, voluntary organization, dedicated to helping children and families who are affected by a disease of neurotransmitter metabolism. The Association is committed to the identification and treatment of all neurotransmitter diseases through education, advocacy, and research.

The Association works with families, physicians, researchers and other health care professionals to promote the following:

- Provide patients and families with information about pediatric neurotransmitter diseases.
- Increase public awareness about pediatric neurotransmitter diseases and to act as a source of information for health care providers.
- Establish and coordinate a communication network among affected families.
- Promote public and private support for pediatric neurotransmitter diseases.

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## Investigational Studies

Kathryn 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. Please contact Dr. Swoboda via her clinical coordinator Mark Wride if you, your patient or a family member are interested in participating in the PND database and related studies. Telephone: 801-585-9717, email [mwride@genetics.utah.edu](mailto:mwride@genetics.utah.edu) or [Swoboda@genetics.utah.edu](mailto:Swoboda@genetics.utah.edu)

## Resources

PND Association - Pediatric Neurotransmitter Disease Association  
[www.pndassoc.org](http://www.pndassoc.org)

The American Board of Medical Genetics website  
[www.faseb.org/genetics/](http://www.faseb.org/genetics/)  
Click on *The American Board of Medical Genetics*

NORD - National Organization for Rare Diseases  
[www.rarediseases.org](http://www.rarediseases.org)

NINDS - National Institute of Neurological Disorders and Stroke  
[www.ninds.nih.gov/](http://www.ninds.nih.gov/)

Exceptional Parent Magazine  
[www.eparent.com](http://www.eparent.com)

The Alliance for Genetic Support Groups  
[www.geneticalliance.org](http://www.geneticalliance.org)

Family Voices  
[www.familyvoices.org](http://www.familyvoices.org)

Free registration, a large searchable database, and periodic updates via e-mail  
[www.medscape.com](http://www.medscape.com)

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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 for many infants and young children with TH Deficiency. It is imperative that the pharmacist compound special doses of L-dopa and carbidopa for children. Children with the TH 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.

In children who are severely affected, 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  
Monoamine Oxidase B Inhibitors - Selegeline  
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 TH 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:

Tyrosine Hydroxylase Deficiency

Key Words: "Tyrosine Hydroxylase"  
Access Listing: 191290

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

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

## What are Neurotransmitters?

Neurotransmitters are chemicals released during a nerve impulse to either excite or inhibit nerve function. There are many neurotransmitters in the body all of which work together to regulate motor coordination, behavior, temperature, pain mechanisms and blood flow.

The neurotransmitters which are involved in these disease groups include the catecholamines (dopamine, norepinephrine, epinephrine), serotonin, and gamma-aminobutyric acid (GABA).

## What are Pediatric Neurotransmitter Diseases?

"Pediatric Neurotransmitter Disease" (PND) is an umbrella term for genetic disorders that affect the synthesis, metabolism and catabolism of neurotransmitters. These inborn errors of metabolism affect the central nervous system in children. Currently the PND Association represents several diseases related to the following neurotransmitters:

### GABA (GAMMA-AMINOBUTYRIC ACID)

- Succinic Semialdehyde Dehydrogenase Deficiency (SSADH)

### DOPAMINE AND SEROTONIN

- Aromatic L Amino Acid Decarboxylase Deficiency (ALADD or AADC)
- Tyrosine Hydroxylase Deficiency (TH Deficiency)
- GTP-1 Cyclohydrolase Deficiency
- Sepiapterin Reductase Deficiency without Hyperphenylalanemia
- Unknown Biogenic Defects

## What is Tyrosine Hydroxylase Deficiency?

Tyrosine Hydroxylase (TH) deficiency (also known as Recessive Dopa-Responsive Dystonia) is a rare metabolic disorder characterized by the lack of the enzyme involved in converting the amino acid tyrosine to L-dopa. TH is a critical enzyme in normal dopamine production. Lack of this enzyme means neurotransmitters are blocked from signaling one another appropriately. The neurotransmitters dopamine, norepinephrine, epinephrine (collectively known as catecholamines) and serotonin are deficient in the central nervous system and periphery.

Patients with TH Deficiency can develop movement disorders, autonomic symptoms (blood pressure instability, temperature irregularities), abnormal eye movements and neurological impairment.

## What symptoms are associated with TH Deficiency?

A wide range of symptoms can be associated with TH Deficiency, and involvement can vary from mild, moderate to severe.

**Mild:** In the mildest cases, walking or running may be clumsy but little

else may be noticed initially. Symptoms may progress slowly as the child gets older. 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. Attention difficulties in school are common. 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. Unusual arm posturing or positions of their arms with attempts to walk or walk on their toes is common. Abnormal eye movements, tremor and speech delay may be present. Children with moderate symptoms often respond well to treatment but full benefit may take many months.

**Severe:** In the most severe cases children are physically disabled and affected from early infancy. This is sometimes known as the Infantile Parkinson's disease variant. 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)
- Intermittent color changes
- Unexplained low body temperatures or fevers
- Low blood sugar
- Difficulty regulating blood pressure

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 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. Symptoms may present or worsen during other illnesses the child might experience.

Children with TH Deficiency are often considered clumsy or uncoordinated and are often initially diagnosed with cerebral palsy.

## What causes TH Deficiency?

TH Deficiency is inherited as an autosomal recessive trait. In recessive disorders, the condition 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 will be a carrier but usually will not show symptoms. The risk of transmitting 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 pregnancy.

## 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. It is suspected that many cases either go unrecognized or misdiagnosed.

## How is TH Deficiency diagnosed?

A diagnosis of TH Deficiency is based upon a two 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 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](http://www.pndassoc.org) or contact Keith Hyland PhD, Director Neurochemistry Laboratory, Institute of Metabolic Disease, Baylor University, 214-820-4533, [Keithhy@BaylorHealth.edu](mailto:Keithhy@BaylorHealth.edu)**

### STAGE 2

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 done via a blood sample and results can take some time. There are again specific guidelines for blood sampling/shipping and adherence is critical to the accurate diagnosis of TH Deficiency. For information on how to collect and where to send the samples, or to receive a testing packet please refer to the above information. If possible samples should be collected from all family members.

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

## How is TH Deficiency treated?

Presently, the most well established treatment of TH Deficiency is