“Hope for tomorrow begins today”

For more information about Pediatric Neurotransmitter Diseases contact us at:

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For more information please visit our Web site: www.pndassoc.org

“A Guide To Tyrosine Hydroxylase Deficiency”

“Hope For Tomorrow Begins Today”
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.

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 or Swoboda@genetics.utah.edu

Resources

PND Association - Pediatric Neurotransmitter Disease Association
www.pndassoc.org

The American Board of Medical Genetics website
www.faseb.org/genetics/
Click on The American Board of Medical Genetics

NORD - National Organization for Rare Diseases
www.rarediseases.org

NINDS - National Institute of Neurological Disorders and Stroke
www.ninds.nih.gov/

Exceptional Parent Magazine
www.eparent.com

The Alliance for Genetic Support Groups
www.geneticalliance.org

Family Voices
www.familyvoices.org

Free registration, a large searchable database, and periodic updates via e-mail
www.medscape.com

“Hope for tomorrow begins today”
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)

DOP AMINE AND SEROTONIN
• Aromatic L Amino Acid Decarboxylase Deficiency (ALADD or AADC)
• Tyrosine Hydroxylase Deficiency (TH Deficiency)
• GTP-1 Cyclohydrolase Deficiency
• Sepiapterin Reducatase 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 tip toes 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.

**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