



A Guide To Aromatic L-Amino Acid Decarboxylase Deficiency

*“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



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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 AADC 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

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is AADC” in the brochure). There are again specific guidelines for blood sampling/shipping and adherence is critical to the accurate diagnosis of AADC. 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 AADC, then consideration should be given to other Pediatric Neurotransmitter Diseases.

How is AADC treated?

Presently treatment of AADC involves a variety of medications with varying success from patient to patient. Medication could include any one or combination of the following:

Dopamine Receptor Agonist
Anticholinergic Agents
Antiepileptics
Monoamine Oxidase Inhibitor
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 Aromatic L-Amino Acid Decarboxylase 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:

Key Words: “Aromatic L-Amino Acid Decarboxylase Deficiency”
Access Listing: 107930

<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 AADC or ALADD?

Aromatic L-Amino Acid Decarboxylase Deficiency (AADC or ALADD) is a rare metabolic disorder, characterized by the lack of the enzyme involved in the decarboxylation of the aromatic amino acids, L-dopa and 5-hydroxytryptophan. 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 AADC suffer from severe movement disorders, abnormal eye movements, autonomic symptoms and neurological impairment.

What symptoms are associated with AADC?

The most common symptom of AADC is referred to as a “Spell” or

“Attack”. Usually they begin in the afternoon and are characterized by increased irritability, crying, abnormal eye movements, stiffness with abnormal posturing and stridor (rattled breathing). These “Spells” or “Attacks” can last for many hours and to the caregiver this may be a frightening time.

Other symptoms associated with AADC may be mild, moderate or severe and often vary greatly from case to case. The symptoms of AADC are caused by low or absent plasma AADC enzyme activity in the brain and include the following manifestations*:

(*Defined as: common >70% of patients; frequent, 30-70% of patients; unusual, <30% of patients).

Common manifestations

- Overall hypotonia (including trunk, head and limbs)
- Rigidity and stiffness
- Abnormal eye movements (crossing, upward fixed gaze, eyes darting side to side)
- Ptosis (droopy eyelids)
- Dystonia
- Paucity of spontaneous movements
- Limb tremor with attempted voluntary movement
- Autonomic dysfunction (blood pressure and body temperature regulation, heart rate fluctuations)
- Excessive sweating
- Dysphoria and emotional lability
- Sleep disturbance (excessive or disrupted)
- Absence of speech
- Irritability and crying
- Stridor (rattled breathing)
- Swallowing and feeding difficulties
- Hypersalivation
- Tongue thrusting
- Gastrointestinal symptoms (dysmotility and absorption, gastroesophageal reflux, constipation and diarrhea)
- Nasal congestion
- Developmental delay
- Hypersensitivity to sensory stimuli
- Increased startle
- Head drops
- Torticollis (involuntary deviation of the head and neck)

Frequent manifestations

- Breathholding or Apneic Spells
- Growth deficiency
- Flexor Spasms
- Orofacial Dystonia

Unusual manifestations

- Endocrine Abnormalities (Hypoglycemia)
- Cardiorespiratory arrest
- Generalized seizures

Children with AADC are often initially diagnosed with Seizure Disorder, Cerebral Palsy, Congenital Myasthenia and Mitochondrial Disorder.

What causes AADC?

AADC 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 AADC?

AADC affects males and females in equal numbers. Only 19 cases have been diagnosed throughout the world. The first diagnosed case of AADC was in 1990, since then, through awareness and education, 15 of the 19 patients have been diagnosed in the last 5-6 years. It is suspected that there are many patients either undiagnosed or misdiagnosed.

How is AADC diagnosed?

A diagnosis of AADC is based upon a two stage testing procedure:

STAGE 1

A lumbar puncture (spinal tap) to determine abnormalities of neurotransmitter metabolites. Screening of the cerebrospinal fluid (CSF) should show the following characteristic results for AADC;

- a) Elevated levels of L-dopa, 5-hydroxytryptophan (%HTP) and 3-orthomethyl-dopa (3-o-md).
- b) Decreased levels of homovanillic acid (HVA) and 5-hydroxyindoleacetic (5HIAA) levels

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 or contact Keith Hyland PhD, Director Neurochemistry Laboratory, Institute of Metabolic Disease, Baylor University, 214-820-4533, Keithhy@BaylorHealth.edu

The results of Stage 1 will determine whether Stage 2 is appropriate.

STAGE 2

Blood samples can determine whether there is low/absent enzyme involved in the decarboxylation of aromatic amino acid. (Refer to “What