

## 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.

*“Hope for tomorrow begins today”*



# A Guide To Succinic Semialdehyde Dehydrogenase Deficiency



Pediatric Neurotransmitter  
Disease Association

*“Hope For Tomorrow Begins Today”*



One day I will walk  
One day I will talk  
Today, I can smile!

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

## 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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## What are Pediatric Neurotransmitter Diseases (PNDs)?

“Pediatric Neurotransmitter Disease” 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-AMINOBRYTRIC)

- Succinic Semialdehyde Dehydrogenase Deficiency (SSADH)

### DOPAMINE AND SEROTONIN

- Aromatic L Amino Acid Decarboxylase (ALADD or AADC)
- Tyrosine Hydroxylase Deficiency (TH Deficiency)
- GTP-1 Cyclohydrolase Deficiency
- Unknown Biogenic Defects

## What is SSADH?

Succinic semialdehyde dehydrogenase deficiency (SSADH) is a rare metabolic disorder characterized by lack of the enzyme involved in the degradation of GABA, the major inhibitory neurotransmitter in the brain. GABA controls the movements of humans, and when it is imbalanced, major neurologic abnormalities occur. In SSADH deficiency, neurotransmitters are blocked from signaling one another correctly.

Due to the enzyme deficiency in SSADH patients, an unusual compound accumulates in the body, namely 4-hydroxybutyric acid (or gamma-hydroxybutyric acid; GHB). GHB is possibly a neurotransmitter like GABA, or at least at high concentrations it is likely a modulator of neurologic activity in humans. GHB accumulation interferes with the patient's ability to walk, speak, concentrate and process information in the brain.

## What symptoms are associated with SSADH?

Symptoms associated with SSADH may be mild, moderate or severe and often vary greatly from case to case. The symptoms of SSADH are caused

by the accumulation of CHB 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

- Delayed gross motor development
- Delayed mental development
- Delayed fine motor skill development
- Delayed speech and language development
- Hypotonia

### Frequent manifestations

- Seizures
- Hyporeflexia
- Ataxia
- Behavioral problems
- Hyperkinesia

### Unusual manifestations

- Neonatal problems
- EEG abnormalities
- Psychoses
- MRI or CT abnormalities
- Oculomotor apraxia
- Microcephaly
- Macrocephaly
- Hyperreflexia
- Somnolence
- Autistic features
- Choreoathetosis
- Myopathy

## What causes SSADH?

SSADH 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 percent. 50 percent of their children risk being

carriers of the disease but generally will show no symptoms of the disorder, 25 percent of their children may receive both normal genes, one from each parent, and will be genetically normal for that trait. The risk is the same for each pregnancy.

## Who gets SSADH?

SSADH deficiency affects males and females in equal numbers. Approximately 350 cases of SSADH have been diagnosed throughout the world. However, it is believed that many SSADH patients are either undiagnosed or misdiagnosed.

## How is SSADH diagnosed?

A diagnosis of SSADH deficiency is made based upon urine organic profiling or blood amino acid analysis. For testing information contact K. Michael Gibson Ph.D. or Phippip Pearl MD. (refer to Investigational Studies).

## How is SSADH treated?

Presently there is no known established and universally effective therapeutic treatment for SSADH deficiency. In the longer term, medical advancements made in gene therapy or stem cell transplantation may provide an avenue to cure the disorder. In the shorter term, several therapies have been tried or are currently being considered as listed below:

- Vigabatrin or Sabril - pharmacologically, the mode of action is an irreversible inhibition of GABA-transaminase, leading to accumulation of free and total GABA in the brain. The results of this therapy have been encouraging in some patients, and of little to no value in others. This medication has been suspended or avoided by some patients due to the potential side effects.
- Lamotrigine - Pharmacologically, the mode of action is to inhibit the release of excitatory amino acids, especially the major GABA precursor glutamate, via inhibition of glutamic acid decarboxylase. Lamotrigine has been successfully used and well tolerated in at least one patient.
- NCS-382 antagonist - clinical trials on the use of this agent is pending.

In addition to the therapies listed above, several medications such as Prozac or Ritalin have been prescribed to assist in controlling behavioral abnormalities. Extensive speech, physical and occupational therapy are strongly encouraged.

## Selected References

For a complete list of articles on SSADH, 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: "Succinic Semialdehyde Dehydrogenase Deficiency"  
Access Listing: 271980

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

## Investigational Studies

K. Michael Gibson, PhD, FACMG, Professor, Department of Molecular and Medical Genetics and Director, Biochemical Genetics Laboratory at Oregon Health & Science University has begun to revolutionize the study of human inborn errors of metabolism through the use of transgenic mice. Disruption of specific genes in mice enable a researcher to study the "human" counterpart disease in a model system (mouse) which produces rapidly. This approach has recently been applied to SSADH deficiency. In November of 1999, the first mice with genetically altered SSADH were born. These new knockout mice are the subject of intense investigation, and new therapeutic approaches are being attempted in them. The development of useful therapeutics will ultimately have important benefits to those with the human disease.

Please contact Dr. Gibson by email at [gibsonm@ohsu.edu](mailto:gibsonm@ohsu.edu) or telephone at (503) 494-2400

Phillip L. Pearl, MD, Associate Professor of Pediatrics and Neurology at The George Washington University School of Medicine and Pediatric Neurologist at The Children's National Medical Center in Washington, DC maintains a SSADH database and is a clinical expert for SSADH deficiency patients.

Please contact Dr. Pearl by email at [ppearl@cnmc.org](mailto:ppearl@cnmc.org) or telephone at (202) 884-2120.