

# **Title: adrenomyelopathy**

Field of study: Diseases and syndromes

*Also known as:*

Adrenoleukodystrophy, Adrenomyeloneuropathy; Addison disease; Childhood cerebral adrenoleukodystrophy; ALD; Schilder-Addison Complex

*Definition*

Adrenomyelopathy is a category and adult form of the disease known as Adrenoleukodystrophy. Adrenoleukodystrophy describes adrenomyelopathy and several other closely related inherited disorders that interrupt the metabolism of very-long-chain fatty acids.

*Risk Factors:*

A family history of adrenoleukodystrophy which is expressed as adrenomyelopathy or related inherited disorders is the primary risk factor for the disease.

*Etiology and Genetics of This Disorder*

The accumulation of long-chain fatty acids in the nervous system, adrenal gland, and testes, results in the disruption of normal activity. The condition is genetically passed down from parents to their children as an X-linked genetic trait. Although mostly males in their 20s or later are affected by adrenomyelopathy some women carriers of the gene can have milder forms of the disease. Approximately 1 in 20,000 people from all races are afflicted with Adrenoleukodystrophy which includes two other major categories of disease. The childhood cerebral form is characterized by a more severe onset of neurological symptoms appearing between 5-12 years of age. The other common category is called impaired adrenal gland function also referred to as Addison disease or Addison-like phenotype in which the adrenal gland does not produce enough steroid hormones. Genetically speaking, the ALD gene is located on the Xq28 region of the X chromosome and contains 10 exons, and spans 20 kb of genomic DNA. The gene codes for a protein called the ALD protein have been localized to the peroxisomal membrane. The gene is subject to X-inactivation placing implications for female (XX) members of a family with an X-linked inherited disorder. This X-inactivation process, in which one of the two X chromosomes becomes condensed and inactive, randomly and permanently occurs at the embryonic stage. If the defective allele is on the chromosome that has been inactivated, there will be no phenotypic manifestation of the disease. However, if the defective allele is on the active X chromosome, the other having been inactivated, there will be a clinical expression of the disorder. Mutation analysis of the ALD gene in 35 unrelated ALD individuals, revealed that all had X-q28 ALD gene mutations within this group, six percent had large deletions, and 17% had an AG deletion in axon 5; the remainder had "private" mutations that were specific for each kindred, of which 55% had missense mutations and 30% had frame-shift mutations; nonsense mutations occurred in 8% and splice defects in 4%. No correlation between the nature of the mutation and the phenotype has been detected.

### *Symptoms*

Symptoms of adrenomyelopathy include adrenal dysfunction, trouble controlling urination, muscle weakness or leg stiffness that may worsen over time, difficulty with visual memory and rapidity of thinking.

### *Screening and Diagnosis*

Laboratory investigation of blood samples may show levels of elevated very-long-chain fatty acids. Peripheral nerve biopsy has revealed characteristic inclusion bodies in the Schwann cells. Chromosome studies can be useful in demonstrating specific gene mutations. Magnetic resonance imaging will reveal images of damaged white matter of the brain

### *Treatment and Therapy*

A specific treatment for X-linked adrenoleukodystrophy is not available, but adrenal dysfunction is often treated with steroids such as cortisol. A diet low in very-long-chain fatty acids is thought to lower the blood levels of very-long-chain fatty acids. Also ingesting oils called Lorenzo's oil, are being tested as a treatment in lowering the blood levels of very-long-chain fatty acids. Bone marrow transplant is also being considered as a potential treatment.

### *Prevention and Outcomes*

Genetic counseling is recommended for potential parents who have a family history of X-linked adrenoleukodystrophy. A test sensitive in denoting very-long-chain fatty acids and a DNA probe study by specialized laboratories can diagnose the carrier state in 85% of the female cases. Prenatal diagnosis of X-linked adrenoleukodystrophy is also available by an amniocentesis. Outcomes of adrenomyelopathy are milder than the childhood form of X-linked adrenoleukodystrophy which is described as progressive and leads to a long-term coma 2 years after neurological symptoms develop.

*Byline:* Jeffrey P Larson PT, ATC

### *Further Reading*

Patricia I. Rosebush, M.Sc.N., M.D., F.R.C.P.C., Sarah Garside, M.D., Ph.D., Anthony J. Levinson, M.A., M.D. and Michael F. Mazurek, M.D., F.R.C.P.C.  
The Neuropsychiatry of Adult-Onset Adrenoleukodystrophy J Neuropsychiatry Clin Neurosci 11:315-327, August 1999

Moser HW: Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. Brain 1997; 120:1485–1508 O'Neill BP, Marmion LC, Feringa ER:

The adrenoleukomyeloneuropathy complex: expression in four generations. *Neurology* 1981; 31:151–156

Moser HW: Adrenoleukodystrophy: natural history, treatment and outcome. *J Inherit Metab Dis* 1995; 18:435–447

Experts Join In Studying Lorenzo's Oil By Gina Kolata *The New York Times* Sunday, September 11, 1994

Korenke GC, Roth C: Variability of endocrinological dysfunction in 55 patients with X-linked adrenoleukodystrophy: clinical, laboratory and genetic findings. *Eur J Endocrinol* 1997; 137:40–47

Moloney JBM, Masterson JG: Detection of adrenoleukodystrophy carriers by means of evoked potentials. *Lancet* 1982; ii:852–853

#### *Web Sites of Interest*

The Endocrine Society <http://www.endo-society.org/>

Endocrineweb <http://www.endocrineweb.com/>

Endocrine associates [www.endocrine-associates.com](http://www.endocrine-associates.com)

The New York Times

<http://health.nytimes.com/health/guides/disease/adrenoleukodystrophy/overview.html>

endocrine abstracts <http://www.endocrine-abstracts.org/index.aspx>

Adrenal Gland Disorders. [www.nichd.nih.gov/health/topics/Adrenal\\_Gland\\_Disorders.cfm](http://www.nichd.nih.gov/health/topics/Adrenal_Gland_Disorders.cfm)

# **Title: pseudohypoparathyroidism**

Field of study: Diseases and syndromes

*Also known as:*

Albright's hereditary osteodystrophy; Types 1A and 1B pseudohypoparathyroidism

*Definition*

Pseudohypoparathyroidism denotes a group of inherited disorders characterized by deficiency in the end-organ response to parathyroid hormone (PTH) and in some instances because of abnormal PTH receptors. The term pseudohypoparathyroidism is used because there is evidence of clinical hypoparathyroidism but serum PTH levels are normal.

*Risk Factors*

A family history of pseudohypoparathyroidism which is expressed as Albright's hereditary osteodystrophy; Types 1A and 1B pseudohypoparathyroidism is the primary risk factor for the disease.

*Etiology and Genetics of This Disorder*

Parathyroid glands assist in the control of calcium use and removal by the body by producing parathyroid hormone, or PTH. PTH helps control calcium, phosphorus, and vitamin D levels within the blood and bone. Individuals with pseudohypoparathyroidism produce the required amount of PTH, but the body is "resistant" to its effect. This causes low blood calcium levels and high blood phosphate levels. Pseudohypoparathyroidism is very rare and is caused by abnormal genes. Type Ia also called Albright's hereditary osteodystrophy, is an inherited autosomal dominant trait and therefore only one parent could potentially pass the defective gene to develop the condition. The condition causes short stature, round face, abnormally developed metacarpal and metatarsal bones and subcutaneous bone ossification. . Type Ib is less understood than type Ia and involves resistance to PTH only in the kidneys. Type II is very similar to type I in its clinical features, but the events that take place in the kidneys are different.

Type 2 pseudohypoparathyroidism also involves low blood calcium and high blood phosphate levels, but persons with this form do not develop the physical characteristics seen in those with Type 1a. Recent studies report the GNAS gene encodes the alpha-

subunit of the stimulatory G proteins. These proteins are important in intracellular signal transduction of peptide and neurotransmitter receptors. Heterozygous inactivating maternally inherited mutations of GNAS lead to a phenotype in which Albright hereditary osteodystrophy is associated with pseudohypoparathyroidism type Ia.. Such mutations include translation initiation mutations, amino acid substitutions, nonsense mutations, splice site mutations and small insertions or deletions. E. Fernandezrebollo and colleagues found the GNAS gene of a 5-year-old boy with pseudohypoparathyroidism to have a heterozygous inversion of exon 2 and part of intron 1 of de novo origin. This report demonstrated the first evidence for an inversion at the GNAS gene responsible for pseudohypoparathyroidism type I

### *Symptoms*

Symptoms of pseudohypoparathyroidism are related to low levels of calcium known as hypocalcemia. Hypocalcemia causes increased irritability of nerves, leading to numbness and tingling of the hands, feet, and lips. Tetany, which is manifested clinically as muscular spasms first affects the hands and feet is another symptom of pseudohypoparathyroidism. Laryngeal spasms can occur leading to obstruction of the respiratory system. Severe hypocalcaemia can lead to generalized convulsions in children. Other complications of hypocalcemia associated with pseudohypoparathyroidism may include other endocrine problems, leading to lowered sexual drive and lowered sexual development, lowered energy levels, and increased weight. Individuals with Albright's hereditary osteodystrophy may have symptoms of calcium deposits under the skin, and physical characteristics of a round face and short neck and short stature in children

### *Screening and Diagnosis*

Blood tests are evaluated to determine calcium, phosphorus, and PTH levels. Urine tests are also utilized to determine key endocrine levels. Genetic testing is utilized to determine positive family history of the abnormalities. Magnetic resonance imaging creates a detailed pictures of the brain and surrounding nerve tissues, and is helpful in diagnosing decreased levels of calcium causing increased irritability of nerve tissue.

### *Treatment and Therapy*

Calcium and vitamin D supplements are prescribed to maintain proper calcium levels. A low-phosphorus diet may be necessary if blood phosphate levels remain higher than normal. Emergency treatment with IV calcium is needed if an individual presents acute hypocalcaemia crisis such as tetany, laryngeal spasm and convulsions.

### *Prevention and Outcomes*

Low blood calcium in pseudohypoparathyroidism is usually milder than in other forms of hypoparathyroidism. Proper medical attention and follow-up is important in prevention and treatment of other endocrine problems as patients with type Ia pseudohypoparathyroidism have an increased occurrence of other endocrine abnormalities to include hypothyroidism and hypogonadism.

*Byline:*

Jeffrey P Larson PT, ATC

*Further Reading*

Copstead, Lee-Ellen. Perspectives on Pathophysiology. WB Saunders Philadelphia, PA. 1994.

Chandrasoma, P and Taylor, C. Concise Pathology. Appleton and Lange. Norwalk Conn. .1991.

Albright's hereditary osteodystrophy. A Dictionary of Nursing. Oxford University Press. 2008.

Study findings from E. Fernandezrebollo et al broaden understanding of pseudohypoparathyroidism." Biotech Week. NewsRX. 2008.

Journal of Clinical Endocrinology and Metabolism 4350 East West Highway, Suite 500, Bethesda, MD 20814-4110, USA.

Wysolmerski JJ, Insogna KL. The Parathyroid Glands, Hypercalcemia, and Hypocalcemia. In: Kronenberg HM, Schlomo M, Polansky KS, Larsen PR, eds. *Williams Textbook of Endocrinology*. 11th ed. St. Louis, Mo: WB Saunders; 2008: chap. 266.  
Bringham FR, Demay MB, Kronenberg HM. Disorders of Mineral Metabolism. In: Kronenberg HM, Schlomo M, Polansky KS, Larsen PR, eds. *Williams Textbook of Endocrinology*. 11th ed. St. Louis, Mo: WB Saunders; 2008: chap. 27.

*Web Sites of Interest*

The Endocrine Society <http://www.endo-society.org>

Endocrineweb <http://www.endocrineweb.com/>

Endocrine associates [www.endocrine-associates.com](http://www.endocrine-associates.com)

HighBeam Research. <http://www.highbeam.com>