



...out of the darkness
into the light...

www.rarediseases.org

55 Kenosia Avenue
PO Box 1968
Danbury, CT 06813-1968
Phone: 203.744.0100
Toll Free: 1-800-999-6673
Fax: 203.798.2291

APS Type-1

The National Organization for Rare Disorders (NORD) web site, its databases, and the contents thereof are copyrighted by NORD. No part of the NORD web site, databases, or the contents may be copied in any way, including but not limited to the following: electronically downloading, storing in a retrieval system, or redistributing for any commercial purposes without the express written permission of NORD. Permission is hereby granted to print one hard copy of the information on an individual disease for your personal use, provided that such content is in no way modified, and the credit for the source (NORD) and NORD's copyright notice are included on the printed copy. Any other electronic reproduction or other printed versions is strictly prohibited.

The information in NORD's Rare Disease Database is for educational purposes only. It should never be used for diagnostic or treatment purposes. If you have questions regarding a medical condition, always seek the advice of your physician or other qualified health professional. NORD's reports provide a brief overview of rare diseases. For more specific information, we encourage you to contact your personal physician or the agencies listed as "Resources" on this report.

Copyright 1991, 1999, 2007, 2008

NORD is very grateful to Noel K. Maclaren, MD, Clinical Professor of Pediatrics, Weill College of Medicine of Cornell University, Director of BioSeek Endocrine Clinics, New York, NY, for his valuable assistance in the preparation of this report.

Synonyms of APS Type-1

- APS 1
- Autoimmune-Polyendocrine-Candidiasis-Ectodermal Dystrophy Syndrome
- Autoimmune Polyendocrinopathy Type I
- PGA Syndrome Type 1
- Polyglandular Autoimmune Syndrome

Disorder Subdivisions

General Discussion

APS-1 is a rare and complex inherited disorder of immune-cell dysfunction with multiple

autoimmunities. It presents as a constellation of symptoms and side-effects with potentially life-threatening endocrine gland and gastro-intestinal dysfunctions. The acronym of APS-1 stands for autoimmune polyglandular syndrome.

A condition is said to be 'autoimmune' when antibodies and immune cells are launched by the body against one or several antigens of its own tissues. Since most of the target antigens have now been discovered, the corresponding auto-antibodies can often be measured in the blood as markers for the ongoing autoimmune disease to which they correspond.

APS-1 is caused by a large number of mutations of the autoimmune regulator (AIRE) gene. (For further information about the AIRE gene, please go to the 'Causes' section of this report.) HLA-DR/DQ genes also play a role in predisposing to which of the component disease the patient actually develops.

Symptoms

While the symptoms of APS-1 are variable in each patient, they will have components of at least two of the three major conditions that are the result of this syndrome: chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenocortical insufficiency.

Chronic mucocutaneous candidiasis (CMC), a condition of recurrent candidiasis infections that may involve the skin, nails, oral, anal and genital mucosa, is a hallmark of APS Type 1 syndrome. It is often the first manifestation of APS Type 1, typically appearing and recurring frequently within the first two years of life. The CMC of APS Type 1 syndrome generally presents in babies as frequent thrush (oral candidiasis), diaper rash, and/or skin rashes. (For further information on CMC, please see 'Related Disorders' section of this report.)

The ectoderm is the outermost layer of the three primary cell layers of a developing embryo. It gives rise to specific tissues, including the skin, teeth, nails, hair and mucous membranes. A 'dystrophy' is a disorder of the structure of an organ or tissue of the body.

The term 'ectodermal dystrophy' refers to the particular abnormalities of the nails, dental enamel (enamel hypoplasia of permanent teeth), hair (alopecia), corneas (keratopathy) and skin (vitiligo--areas of depigmentation of the skin) that may be seen in patients with APS Type 1. These findings are not all necessarily present in every patient with APS Type 1, but can develop as a result of specific AIRE mutations. However, alopecia and vitiligo are caused by other specific autoimmunities, while nail deformities result from chronic candidiasis. The cause of dental enamel hypoplasia in APS Type 1, however, has not yet been determined. Metaphyseal dysplasias of the lower limb bones have recently been also described.

Patients with APS Type 1 have a defect of the immune system involving a particular subset of T-cells called 'Treg' (T-regulatory) cells. It is suggested that this Treg-cell defect leads to the wide spread loss of immune tolerance, causing the autoimmunities in the disease. However, a specific defect in immunity to candidiasis indicates the present of

an immune effector defect also. Possibly, the invariable presence of auto-antibodies to the interferon family of immunological molecules called cytokines may prove to be the underlying reason.

The first endocrine gland dysfunction to occur in APS Type 1 is usually hypoparathyroidism (under functioning of the parathyroid glands). More than 75% of patients develop hypoparathyroidism, usually before age 10-years. Dysfunction of the parathyroid glands leads to below-normal of serum calcium together with elevated phosphorus levels. In turn, this can lead to a host of clinical findings, including muscle cramping and spasms, rigidity (tetany) and eventually, seizures. (For further information on hypoparathyroidism, see Related Disorders Section of this report.)

Adrenocortical insufficiency (Addison's disease) is typically the second endocrine disorder to appear in APS-1. Adrenocortical insufficiency is a disorder characterized by chronic and insufficient functioning of the cortex (outer layer) of the adrenal gland. This malfunction results in a deficiency of the glucocorticoid and salt retaining hormones cortisol and aldosterone respectively. Deficiencies of these hormones may lead to diarrhea, nausea and vomiting, low blood pressure, dehydration, and a small-sized heart. These side-effects can become pronounced and life-threatening if not correctly identified and treated. (For further information on adrenocortical insufficiency, see Related Disorders Section of this report.)

Patients with APS-1 can also develop other endocrine disorders, including autoimmune liver disease (chronic active hepatitis), ovarian/testicular failure (hypogonadism), early onset pernicious anemia from atrophic gastritis, and a variety of gastro-intestinal problems resulting in chronic malabsorption and diarrhea. Insulin-dependent diabetes may also occur, albeit more often in Scandinavian patients than is seen in the US.

Causes

APS Type 1 is the result of autosomal recessive genetic transmission of mutations of a single gene. This gene is called the 'AIRE' gene. To date, more than 60 mutations in the AIRE gene have been identified in people with APS Type 1.

Recessive genetic disorders occur when an individual inherits two copies of an abnormal gene for the same trait, one from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease but will not show symptoms. The risk for two carrier parents to both pass the defective gene and have an affected child is 25% with each pregnancy. The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The chance for a child to receive normal genes from both parents and be genetically normal for that particular trait is 25%. The risk is the same for males and females.

All individuals carry many abnormal single copy genes. Parents who are close relatives (consanguineous) have a higher chance than unrelated parents to both carry the same abnormal gene, which increases the risk to have children with a recessive genetic disorder. This risk rises with each generation that indulges in first cousin marriages.

The AIRE gene leads to the production of a protein called 'autoimmune regulator' which is highly expressed in the thymus gland, which is the random generator of thymus derived or T lymphocytes. If there is a deficiency of this protein, then those T-cells which have receptors capable of interacting with self antigens can escape into the circulation (instead of being destroyed in the thymus and not released) and result in autoimmune status. For reasons that are still unclear, defects of the autoimmune regulator protein primarily affect endocrine (hormone-producing) glands.

Affected Populations

APS Type I is a very rare disorder that tends to cluster in certain homogenous populations, including certain groups of Finns, Iranian Jews, and Sardinians. However, it can be found in numerous populations and among multiple ethnic groups. In the US, APS-1 probably affects as few as 1 in every 2-3 million newborns

Related Disorders

The following disorders, which are components of APS Type 1, can also occur on their own, separate from the diagnosis of APS Type 1:

Chronic Mucocutaneous Candidiasis (CMC)

CMC refers to a condition of persistent or recurrent yeast infections of the skin, nails, and mucous membranes. The most prevalent of these organisms is *Candida albicans*. When significant CMC occurs, it is often a sign of an underlying T cell disorder, including APS-1. Fortunately the conazole class of drugs has made this disease more easily managed than in former years. *Candida* is a yeast that is part of the normal flora of the gastrointestinal tract, skin, and mucous membranes. Healthy, intact skin and an intact immune system usually provide effective barriers.

People with CMC present with recurrent or persistent candidiasis infections of the oral cavity (thrush) and other mucous membranes, but often have more extensive involvement. The nails may be markedly thickened and discolored with significant swelling of the surrounding tissue. The scalp may be involved, leading to alopecia in areas of scarring. There may be esophageal candidiasis also. Oropharyngeal cancers and cancers of the stomach and tongue occur at increased frequencies in APS-1.

CMC is definitively diagnosed by the presence of *Candida* on fungal skin scrapings.

Hypoparathyroidism

Hypoparathyroidism is a condition characterized by insufficient production of parathyroid hormones by the parathyroid glands, the small, oval glands located behind the thyroid gland in the neck. Parathyroid hormones (along with vitamin D) play a role in regulating levels of calcium in the blood. Due to a deficiency of parathyroid hormones, affected individuals exhibit abnormally low levels of calcium in the blood (hypocalcaemia).

Symptoms and findings associated with hypoparathyroidism may include weakness, muscle cramps, excessive nervousness, headaches, and/or increased excitability (hyper excitability) of nerves. This can lead to uncontrollable twitching and cramping spasms of certain muscles such as those of the hands, feet, arms, and/or face (tetany).

Hypoparathyroidism in APS-1 disease has an autoimmune cause, but it can occur as a separate disorder associated with maldevelopment of the thymus, aortic arch and parathyroid glands (DiGeorge Syndrome) or may also be an inherited disorder. While an antibody to antigens present on the surface of parathyroid cells (the calcium sensing receptor) had previously been reported, more recently, researchers from University Hospital in Uppsala, Sweden have isolated another auto antigen involved in the hypoparathyroidism of APS-1

Chronic Adrenocortical Insufficiency (Addison's Disease)

Addison's disease is a rare disorder characterized by chronic, usually progressive, inadequate production of the steroid hormones cortisol and aldosterone by the outer layer of cells of the adrenal glands (adrenal cortex). Classical Addison's disease is a consequence of the loss of both of these hormones.

Cortisol affects carbohydrate metabolism, connective tissue development, and the amount of water in the body. Aldosterone affects the sodium and potassium equilibrium in the body. When these hormone levels are subnormal, blood pressure and blood volume drop due to increased excretion of salt and thereby water. Dehydration can occur. Major symptoms of Addison's disease include fatigue, weakness, gastrointestinal discomfort, and changes in skin color (hyperpigmentation). Electrolyte disturbances include elevations in serum potassium and low serum sodium levels. Adrenal autoimmunity is associated with auto antibodies against an adrenocortical enzyme named 21-hydroxylase.

An acute, life-threatening state of extreme insufficiency of adrenocortical hormones (Addisonian crisis) may occur in the form of a sudden loss of strength, severe pain in the abdomen or lower back, and/or kidney failure.

Hypogonadism: Females with APS-1 usually develop significant ovarian failures associated with auto antibodies against the side chain cleavage and 17 alpha hydroxylase enzymes of the ovaries. Infertility problems result.

Additional concerns with APS-1:

Auto immunities can also involve the anterior pituitary gland (hypophysitis), the gastric mucosa (antibodies seen includes parietal cell antibodies or antibodies against the hydrogen-potassium ATPase enzyme, and intrinsic factor binding proteins), celiac disease (antibodies against tissue transglutaminase enzyme of the intestinal mucosa), the serotonin rich cells of the small intestine (antibodies against the tryptophan hydroxylase enzyme), and interons as mentioned above.

Many patients are born with hypoplastic spleens, leaving them subject to septicemia. The predisposition to GI cancers, especially involving the tongue, was also mentioned above.

Standard Therapies

Diagnosis

APS-1 is diagnosed definitively through DNA analysis (via blood test) of mutations in the AIRE gene. The diagnosis should be considered in people under 30 years of age who present with at least two of the three typical disease components (CMC, hypoparathyroidism, and/or Addison's disease). . Since virtually all APS-1 patients have interferon auto antibodies, such antibodies when more freely available will serve as a cheaper diagnostic test.

A clinical history and physical exam that suggests more than one endocrine disorder, with or without CMC, should prompt the physician to obtain serum endocrine autoantibody blood tests

@Treatment@

Treatment of APS-1 Syndrome is currently directed toward the specific diseases that are apparent in each patient. In general, replacement therapy of the endocrine hormones that may be lacking, and patient education about the signs and symptoms of these deficiencies, are integral to treatment success. The educational aspect is of extreme importance, as this allows the patient to self-monitor, hopefully avoiding a life-threatening situation.

Addison's disease is treated with drugs such as hydrocortisone and fludrocortisone to replace the cortisol and aldosterone that are deficient in Addison's patients.

Hypoparathyroidism is treated with oral calcium supplements and activated forms (1, 25 dihydroxy) of vitamin D such as Calctriol or Rocaltrol.

For chronic mucocutaneous candidiasis, oral fluconazole (Diflucan) is prescribed.

Investigational Therapies

EURO-THYMAIDE is the first European Research Integrated Project (IP) aimed at understanding the mechanisms underlying the development of autoimmune diseases, by exploring the major biological functions of the thymus.

Euro-Thymaide's approach is mainly based on the major biological function of the thymus i.e. the generation of a repertoire of T cell receptors that are self-tolerant).

Information about this consortium can be found at: <http://www.eurothymaide.org>.

EURAPS is a European physician consortium funded by the European Union. Its mission is to increase knowledge on APS Type 1, in particular, and on autoimmune diseases in general. Their major aims are to create a European registry and biobank that will describe the clinical manifestations of APS Type 1 in detail and to study the natural course of the disease.

Information about EURAPS can be found at: <http://www.apeced.net/>.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Tollfree: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

For information about clinical trials sponsored by private sources, contact:
www.centerwatch.com

Organizations related to APS Type-1

- APS Type1.org

18 Rolling Hill Drive
Morristown NJ 07960
Phone #: 9738869137
800 #: N/A
e-mail: todd.talarico@novartis.com or htalarico@verizon.net
Home page: <http://www.apstype1.org>

- American Autoimmune Related Diseases Association, Inc.

22100 Gratiot Avenue
Eastpointe MI 48021-2227
Phone #: 5867763900
800 #: 8005984668
e-mail: aarda@aarda.org
Home page: <http://www.aarda.org/>

- Endocrine Society

The Endocrine Society
Chevy Chase MD 20815
Phone #: 3019410200
800 #: 8004676663
e-mail: endostaff@endo-society.org
Home page: <http://www.endo-society.org>

- Hypoparathyroidism Association, Inc.

PO Box 2258
Idaho Falls ID 83403
Phone #: 2085243857
800 #:

e-mail: hpth@hpth.org; hpth@cableone.net
Home page: <http://www.hpth.org>

- National Adrenal Diseases Foundation

505 Northern Boulevard
Great Neck NY 11021
Phone #: 5164874992
800 #:
e-mail: NADFmail@aol.com
Home page: <http://www.medhelp.org/nadf>

References

Textbooks

Halonen M, Perheentupa J, Peltonen-Palotie L. Autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy. In: Ochs HD, Puck JM, Smith CI, eds. Primary Immune Deficiency Diseases. 2nd ed. New York, NY: Oxford University Press; 2007:342-351.

Journal Articles

Neufeld, M.; Maclaren, N.; and Blizzard, M.: Autoimmune poly-glandular syndromes. *Pediatr Annals* 9(4), 1980, p. 154-162.

Neufeld, M.; Maclaren, N.; and Blizzard, R.: Two types of autoimmune Addison's disease associated with different poly-glandular autoimmune (PGA) syndromes. *Medicine* 60, 1981, p. 355-362.

Song, Y-H.; Connor, E.; Li, Y.; Zorovich, B.; Balducci, P.; Maclaren, N.K.: Tyrosinase is an auto antigen in autoimmune vitiligo. *Lancet*, 1994, 344:1049-1052.

Li, Y., Song, Y-H., Rais, N., Connor, E., Schatz, D., Muir, A., Maclaren, N. Auto antibodies to the extracellular domain of the calcium sensing receptor in patients with acquired hypoparathyroidism. *J Clin Invest* 1996, 97(4), 910-914.

Song, Y-H.; Connor, E.L.; Muir, A.; She, J.X.; Zorovich, B.; Brooks, D.; Maclaren, N.: Autoantibody epitope mapping of the 21-hydroxylase antigen in autoimmune Addison Disease. *J of Clin Endo and Metab*, 1993, 78(5):1108-1112.

62. Endocrinology: Chen, QY; Kukreja, A; Maclaren, NK; Autoimmune Polyglandular Syndromes. In Eds. DeGroot, L.J. Philadelphia 1999

Alimohammadi M, Björklund P, et al. Autoimmune polyendocrine syndrome type 1 and NALP5, a parathyroid auto antigen. *N Engl J Medicine* 2008 Mar 6; 358(10):1018-28.

LeBoeuf N, Garg A, Worobec S. The autoimmune polyendocrinopathy-candidiasis-

ectodermal dystrophy syndrome [abstract]. *Pediatr Dermatol*, 2007 Sep-Oct;24(5): 529-33.

López MM, Bouthelier R, Cervino E, et al. AIRE gene mutation in polyglandular syndrome type 1 [abstract]. *An Pediatr* 2006 Jun; 64(6): 583-587.

López MM, Bouthelier R, Cervino E, et al. AIRE gene mutation in polyglandular syndrome type 1 [abstract]. *An Pediatr* 2006 Jun; 64(6): 583-587.

Perheentupa J. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [abstract]. *J Clin Endocrinol Metab*. 2006 Aug;91(8): 2843-50.

Proust-Lemoine E, Wémeau JL. APECED syndrome or autoimmune polyendocrine syndrome type 1 [published online ahead of print February 22, 08]. *Presse Med*.

Aldasouqi SA., Akinsot, O., Jabbour SA. Polyglandular autoimmune syndrome. <http://www.emedicine.com/med/TOPIC1867.HTM>. Updated 9/06. Accessed 4/08. McKusick VA, Ed. ONLINE MENDELIAN INHERITANCE IN MAN (OMIM).

The Johns Hopkins University, Autoimmune Polyendocrinopathy Syndrome, Type I. Entry Number: 240300. Last edit date: 3/26/08. Available at <http://www.ncbi.nlm.nih.gov>. Accessed 3/08.

Robles, DT., Hornung, RL., Olson, JM. Candidiasis, chronic mucocutaneous. <http://www.emedicine.com/DERM/topic569.htm>. Updated 1/08. Accessed 3/08.

This information is provided by the National Organization for Rare Disorders (NORD).