Autoimmune lymphoproliferative syndrome (ALPS), which is also known as Canale-Smith syndrome, is an autoimmune syndrome first described by Canale and Smith in 1967. Autoimmune lymphoproliferative syndrome is caused by genetic mutations that interfere with apoptosis or programmed cell death. Normally, all of the body’s cells have a programmed cell death or survival time known as apoptosis. And normally, apoptosis prevents the accumulation of mature lymphocytes.

By destroying mature lymphocytes, apoptosis directly prevents autoimmunity because mature lymphocytes are more likely to become autoreactive and react with the body’s own proteins. However, when there are accumulations of the protein osteopontin or genetic mutations that interfere with apoptosis, the stage is set for the development of autoimmune diseases.

Who is Affected?

People of all ages have been described as having autoimmune lymphoproliferative syndrome, and people of all races are affected. Males and females are affected equally. There are two distinct subtypes of ALPS, a severe disorder that emergences in neonates and children younger than 5 years, and an delayed-onset milder form of ALPS that develops in adults.

Signs and Symptoms in ALPS

Signs and symptoms in autoimmune lymphoproliferative syndrome include moderate to massive splenomegaly (enlarged spleen), skin rashes, frequent nosebleeds, enlarged lymph nodes especially in the neck, enlarged liver, petechia (small bruises), edema, evidence of autoimmunity expressed usually as autoimmune hemolytic anemia, increased levels of gamma immunoglobulins (hypergammaglobulinemia), B-cell lymphocytosis (increased number of B-lymphocytes), thrombocytopenia (decreased platelets), autoimmune neutropenia (decreased number of segmented granulocytes), and the expansion of an unusual population of CD4-CD8- T cells (lymphocytes with markers for T-helper and T-suppressor functions) that express the alpha/beta T-cell receptor (TCR).

ALPS and Other Autoimmune Disorders
Patients with ALPS have been reported to develop a wide array of other autoimmune disorders including Guillain-Barre syndrome, uveitis, systemic lupus erythematosus, and glomerulonephritis. Similarly, patients with autoimmune disorders are known to develop ALPS. Studies suggest that a number of patients with autoimmune disease also have ALPS. In fact, patients with Graves’ disease also have altered levels of soluble Fas, suggesting a genetic connection.

Similar to other autoimmune diseases and syndromes, patients may exhibit symptoms ranging from mild to severe, and periods of remission alternate with periods in which there are variable symptoms. ALPS often resolves by the time affected children reach their teens.

**Immune System in ALPS**

Normally, the cell surface protein Fas (CD95) and its attached ligand protein are instrumental in regulating lymphocyte apoptosis. Consequently, defective expression of either Fas or Fas ligand results in an accumulation of mature lymphocytes. Studies show that mutations of the Fas gene result in a severe form of autoimmune lymphoproliferative syndrome.

The immune system in autoimmune lymphoproliferative syndrome shows a prominent increase in T-helper (CD8) lymphocytes relative to T-suppressor cells, which contributes to autoimmune disease development. The increased number of B-lymphocytes is suspected of contributing to a heightened risk for lymphoma. Individuals with ALPS also have an increased risk, approximately 15-50 times more than normal individuals, of developing lymphoma, which is a cancer of the lymphoid tissues.

Similar to patients with the autoimmune disorder celiac disease, individuals with ALPS generally develop lymphoma many years after their initial diagnosis. While the risk of developing lymphoma is increased in individuals with ALPS, the risk is still rare. In a recent NIH study, of 130 patients diagnosed with ALPS, only 10 patients developed lymphoma. The discovery of this syndrome suggests that therapies directed at the genes that control apoptosis would work for both ALPS and some forms of autoimmune disease.

**Genetic Mutations in ALPS**

Various subsets of ALPS have been described on the basis of the specific mutation found. ALPS Type 1A is caused by a mutation in the FAS gene and ALPS type IB is caused by mutation in the FAS ligand. Type IIA ALPS is caused by mutation in the caspase-10 gene. Type IIB ALPS is caused by mutations in the CASP8 gene. Type III ALPS comprises cases in which a mutation has not been identified. ALPS Type 1A is caused by a mutation in the FAS gene and ALPS type IB is caused by mutation in the FAS ligand. Type IIA ALPS is caused by mutation in the caspase-10 gene. Type IIB ALPS is caused by mutations in the CASP8 gene. Type III ALPS comprises cases in which a mutation...
has not been identified. ALPS Type 0 is characterized by a deficiency of Fas and is caused by homozygous null mutations.

**Treatment**

Treatment for ALPS generally consists of corticosteroids or immunosuppressants such as cyclosporine. However, specific treatments are used depending on the predominant symptoms. Because ALPS is a relatively new syndrome, ongoing clinical trials are researching new therapies.

**Resources:**


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