All about APDS

A quick guide to Activated PI3K Delta Syndrome

What is APDS?

APDS (previously known as PASLI* Disease) is a rare, primary immunodeficiency disease that was first discovered in 2013[1]. It is caused by genetic variants in either one of two identified genes known as PIK3CD or PIK3R1, which are vital to the normal function and differentiation of immune cells in the body.[2]

Impact on people with APDS

APDS has potential life-threatening complications if left under- treated, misdiagnosed or undiagnosed completely.

Symptoms of APDS can vary, even within families carrying the same condition. These can range from asymptomatic adult patients, to those with primary antibody deficiencies, profound immunodeficiencies (which can cause early death), autoimmunities, or patients suffering from lymphoproliferation and malignancy. Most commonly, manifestations begin in early childhood with recurrent respiratory infections, often bronchiectasis (scarring of the airways) and autoimmunity in later childhood.[3]

According to Nicholas Hartog, MD**, “Typically, a person with APDS will present to a hospital within the first 5 years of life with a predominant and recurring respiratory tract infection. They can also present with swollen lymph nodes. Unfortunately, these general patient symptoms often result in medical professionals pre-diagnosing a range of autoimmune disorders before a Primary Immunodeficiency (PI) diagnosis is considered. Even if a PI Classification is given, a patient can be misdiagnosed with Common Variable Immune Deficiency (CVID) and Hyper-IgM. This leads to APDS patients being cared for by a variety of physicians, and managed by treatments that don’t address the underlying genetic defect.”

Common Symptoms in APDS patients[2]

While symptoms can vary, APDS should be considered in patients with the following commonly experienced clinical features:

- Recurrent respiratory tract infections (pneumonia, sinus and ear infections)
- Persistent swollen or enlarged lymph nodes
- Bronchiectasis (scarring of airways)
- Herpesvirus infections:
  - Epstein–Barr virus (EBV)
  - Cytomegalovirus (CMV)
  - Herpes Simplex virus (HSV)
  - Varicella-Zoster virus (VZV)
- An enlarged spleen
- Autoimmune or autoinflammatory conditions (cytopenias)
- Developmental delay (speech and growth)
- Lymphoma (Cancer of the immune system)

Diagnosis of APDS is based on signs and symptoms of the patient and includes laboratory tests (B and T cell activity) along with appropriate genetic testing.

* PASLI (p110δ-activating variation causing senescent T cells, lymphadenopathy, and immunodeficiency)
** Nicholas Hartog, MD, is board certified in pediatric and adult allergy and immunology.

Correct diagnosis may offer new hope and better clinical outcomes for patients with APDS

Testing for APDS

APDS is inherited in an autosomal dominant manner, meaning that a person needs an abnormal gene from only one parent to potentially have it themselves. Other family members may also show similar or the same related medical conditions.[4]

A blood test can identify abnormal changes in B and T cells. This combined with other lab abnormalities and multiple symptoms should raise suspicion and be followed up with a genetic test to diagnose APDS.

APDS Genetic Testing Program

www.invitae.com/en/individuals/diagnostic-genetic-testing/rare-diseases

Current Treatment and Management[5]

Management and treatment of APDS varies from patient to patient and depends on the symptoms present and disease severity. Antibiotics and antivirals are often given to treat or prevent recurrent infections.

The majority of patients have antibody deficiencies and receive immunoglobulin replacement therapy (IRT) given subcutaneously or intravenously. mTor inhibitors such as sirolimus (rapamycin) have been utilized as an attempt to resolve the defective pathways which cause lymphoproliferation.

Rituximab is one of many immuno-suppressive treatments used for autoimmune complications.

For the most severe patients with life threatening complications, hematopoietic stem cell tranplantation (HSCT) has been used to correct the underlying dysfunction though with a high benefit/risk consideration.

Selective PI3K-delta inhibitors are currently being studied in clinical trials and have the potential in the future to offer a targeted treatment option for APDS patients.

Leniolisib (CDZ173), an investigational drug not yet approved by the US Food and Drug Administration (FDA), is an oral selective PI3K-delta inhibitor currently under investigation for the treatment of APDS.

Diagnosing APDS

Laboratory findings and flow cytometry to access T and B cell function/morphology[2,3]

- Low to normal concentrations of IgG and IgA
- Normal or elevated concentration of IgM
- Reversed CD4/CD8 ratio
- Decreased naïve T lymphocytes CD4+ (CD4+CD45RA+) and CD8+ (CD8+CD45RA+)
- Reduced T-helper cells (CD3+ CD4+)
- Increased Transient B-Cells
- Reduced B-Cell (CD19+)

Differential Diagnosis

According to Dr Nicholas Hartog “Patients may have multiple complications though lack a unified diagnosis”.

Some individuals may be misdiagnosed with Common Variable Immunodeficiency (CVID) or Combined Immunodeficiency (CID) and Hyper IgM.

Other patients with APDS can also develop autoimmune and inflammatory complications. These patients may be being treated with various immunosuppressive therapies.

GENETIC TESTING WILL DIAGNOSE APDS

Family Variant Testing is recommended for family members of patients that have been positively identified.

Phase 3 Clinical Trial for Leniolisib is now recruiting.

Leniolisib, an oral selective PI3K-delta inhibitor, is currently being investigated in patients with APDS.

If you are a physician and would like more information or are interested in participating in clinical trials, please visit **www.pharmingclinicaltrials.com**

KEEP UP TO DATE

If you are a patient or caregiver and would like ongoing information about APDS events, insights, news and education, register your details here:

www.pharmingapds.com

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