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PRIMARY **IMMUNODEFICIENCIES**

APDS – ACTIVATED PI3K DELTA SYNDROME

ABBREVIATIONS

APDS	Activated PI3K delta syndrome
CMV	Cytomegalovirus
CVID	Common Variable Immune Deficiency
EBV	Epstein-Barr virus
HSCT	Haematopoietic stem cell transplantation
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PID	Primary immunodeficiency
PI3K	Phosphatidylinositol 3-kinase

Primary immunodeficiencies and APDS

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INTRODUCTION

This booklet explains what Activated PI3K Delta Syndrome (APDS) is, how it is diagnosed, what treatment options are available and ways to manage the disease.

Primary immunodeficiencies (PIDs) are rare diseases that occur when certain parts of the immune system are either missing or not working properly. The immune system protects the body from infections, allergies and other conditions. When the immune system is not working properly, patients with PIDs are more likely to get these conditions.

Activated PI3K delta syndrome (APDS) is a PID where white blood cells in the immune system don't work correctly, particularly ones that are called B cells and T cells. Normally, these cells recognise and attack viruses and bacteria to prevent infection. In APDS, the white blood cells are abnormal so these patients often have frequent infections in the lungs, nose (sinuses) and ears, and can be at greater risk of developing conditions linked with the overproduction of white blood cells (such as swollen lymph nodes and lymphoma).

The following sections explain what APDS is, how it is diagnosed, the symptoms, the long-term effects of the condition, what treatment options are available and ways to manage the disease.

WHAT IS APDS?

Activated PI3K delta syndrome (APDS) is a PID that affects the immune system. The disorder is characterised by white blood cells not working properly, particularly white blood cells called lymphocytes (and especially lymphocytes called B cells and T cells). APDS has also been called PASLI (p110 delta activating mutation causing senescent (old) T cells, lymphadenopathy, and immunodeficiency). It is a rare genetic PID and affects less than 1 in 1,000,000 people.

White blood cells (B cells and T cells) normally recognise and attack viruses and bacteria to prevent infection. Not everyone with APDS is affected to the same extent; some might only experience a few symptoms while others are more affected. APDS usually starts in childhood and is first seen as frequent infections, particularly of the lungs, nose (sinuses) and ears. Over time, repeated lung infections can lead to a condition called bronchiectasis, in which the airways of the lungs become damaged and wider than normal, which leads to a build-up of mucus that can cause breathing problems and make the lungs even more prone to infection. One of the most common symptoms of bronchiectasis is a persistent cough that usually brings up phlegm (sputum). People with APDS may also have viral infections such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infections.

APDS occurs because of a change (mutation) in either one of two genes [called *PIK3CD* (APDS1) or *PIK3R1* (APDS2)]. These genes are involved in making parts of a protein [the p110-delta or the p85 subunit of the phosphatidylinositol 3-kinase (PI3K) enzyme] that is involved in the growth and division (proliferation) of white blood cells (B cells and T cells). The changes, or mutations, found in these genes lead to the creation of an enzyme that is more active than normal (overactive). Unfortunately, this overactive enzyme means the development and control of B cells and T cells is abnormal so their ability to fight off bacterial and viral infections is reduced.

In addition to the abnormal development and control of B cells and T cells, this overactive enzyme in APDS also results in white blood cells being produced faster than normal. This leads to these cells clumping together in small glands in the body called lymph nodes and the nodes becoming enlarged (clinically this is known as lymphadenopathy). These clumps, or dense collections, of cells in the lymph nodes (clinically called nodule lymphoid hyperplasia) usually occur in the airways or intestines of affected individuals. While some of these conditions are non-cancerous (benign; such as lymphadenopathy and nodule lymphoid hyperplasia), APDS does increase the risk of developing a form of blood cancer called B-cell lymphoma.

The abnormal B cells and T cells can also mistakenly attack normal body cells (this is known as autoimmunity), which may result in conditions such as anemia or low platelet counts where the body cannot form blood clots and can cause severe bleeding.

The genes that lead to APDS are inherited, which means that other family members might also have the same genetic fault, so they could show similar or the same related medical conditions.

HOW IS APDS DIAGNOSED?

The diagnosis of APDS is based on the signs or symptoms that an individual displays, laboratory tests (counting the number of different types of lymphocytes such as B cells and T cells), and genetic testing (genotyping).

Clinical presentation: Patients with APDS may present in childhood or later in life with severe, persistent and recurrent bacterial and viral infections, usually in the lungs, nose or ears, a persistent cough that usually brings up phlegm, badly swollen lymph nodes, and often with an enlarged spleen and liver. Young patients may be delayed in their development, and all patients might show signs of autoimmunity and inflammatory conditions. These can include anemia, low platelet counts, inflammation of the colon (colitis, often seen as persistent diarrhea and long-term abdominal pain), and inflammation of the kidneys (glomerulonephritis, seen as pink or brown urine and swelling of the hands, feet, face and abdomen).

Laboratory tests: As a result of the abnormal production of white blood cells there are increased blood levels of old T cells in patients with APDS. Despite the large number of white blood cells, these cells do not function normally and this results in a decrease in the production of antibodies called immunoglobulins in the plasma (clinically known as hypogammaglobulinemia), which fight bacteria and viruses. This decrease in the plasma immunoglobulin level is often seen in another PID called Common Variable Immune Deficiency (CVID). So, it is important to do further tests in patients with CVID that have additional signs or symptoms such as autoimmunity or swollen lymph nodes as it is possible these patients could have APDS. In some cases, APDS can mimic another PID called Hyper-IgM Syndrome.

Genetic testing: Sequencing the genes known to be involved in APDS provides a definitive diagnosis of the disease.

WHAT TREATMENT IS SUGGESTED FOR APDS?

Treatment for patients with APDS depends on their individual symptoms. Infections should be managed quickly with antibiotic (bacterial infections) or antiviral (viral infections) drugs. If patients are at high risk of repeated infections, on-going antibiotic or antiviral drugs may be considered to prevent infections from occurring.

For patients with poor antibody production, immunoglobulin replacement treatment may be used. Here, immunoglobulin preparations are taken from the blood and plasma of healthy donors, purified and then given to the person with APDS. They may be given by either intravenous (into a vein) or subcutaneous (under the skin) injection. The aim of immunoglobulin replacement therapy is to prevent infections and protect the person from possible further infections which can result in damage to organs, such as the lungs, potentially leading to difficulties in breathing.

Haematopoietic stem cell transplantation (HSCT) is the only curative option and, given the risks, may be considered for patients with severe APDS (including for those who have developed a lymphoma). In HSCT, cells that grow to become lymphocytes (called haematopoietic stem cells) are taken from a suitable healthy donor with a good tissue match and are given to the APDS patient replacing the abnormal haematopoietic stem cells and ultimately produce normal immune cells (i.e. B cells and T cells).

Some drugs (such as steroids, sirolimus or the monoclonal antibody rituximab) are able to modify the response of the immune system so they are suitable for patients with features of autoimmunity such as low numbers of blood cells, kidney disease, arthritis, or inflammation of the colon.

Currently ‘targeted therapies’ are being developed (clinical trials ongoing) that specifically target the overactive enzyme (PI3Kdelta inhibitors) and these may prove potentially useful in the treatment of conditions linked with the excessive production of white blood cells (lymphoproliferation).

For more information on ongoing clinical trial please visit: **clinicaltrials.gov** and **clinicaltrialsregister.eu/**

Supportive care when someone has an infection can include: the provision of fluids to avoid dehydration, medicines to reduce fever and pain, bronchodilators to improve breathing, medicine to reduce coughing (anti-tussives), deep breathing exercises and other respiratory treatments such as chest or sinus drainage or chest physiotherapy.

LIVING WITH APDS

The lifestyle adjustments required for patients with APDS will depend on the severity of the symptoms each individual has. For those badly affected and not on immunoglobulin replacement therapy, vaccinations should be kept up to date according to the PID expert physician’s recommendations. Exposure to potential bacteria and viruses that could cause infection should be minimised through personal, food and environmental hygiene, taking precautions when swimming (avoiding lakes/ponds) or having contact with dirt, soil or animals, and avoiding contact with people with infections. Regular checks for swollen lymph nodes and the start of signs and symptoms of lymphoma (high temperature, night sweats, tiredness, itching and unexplained weight loss) should be performed.

FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations in 68 countries worldwide, please visit **www.ipopi.org**.

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Supporting families affected by primary and secondary immunodeficiency

Immunodeficiency UK is a national organisation supporting individuals and families affected by primary and secondary immunodeficiency.

We are the UK national member of IPOPI, an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for PID patients worldwide.

Our website has useful information on a range of conditions and topics, and explains the work we do to ensure the voice of patients with primary and secondary immunodeficiency is heard. If we can be of any help, please email us or call on the number above, where you can leave a message.

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