An Overview of Activated PI3K Delta Syndrome (APDS)

for Patients and Caregivers

Overview of Primary Immunodeficiencies

Primary immunodeficiencies (PIs) are a group of disorders characterized by a weakened or absent immune system. Unlike secondary immunodeficiencies, which are acquired later in life due to factors such as infections, medications, or other medical conditions, primary immunodeficiencies are usually present from birth and result from genetic mutations that affect the development or function of immune cells.

Primary Immunodeficiencies are genetically determined, and they may occur alone or as part of a syndrome. In 2022, the International Union of Immunological Societies reported that 485 inborn errors of immunity (IEIs) – genetic changes – have been linked to primary immunodeficiency disorders - and more are being defined every year [1].

Activated PI3K delta syndrome (APDS) is a rare primary immunodeficiency (PI) that was first discovered in 2013. It is caused by genetic variants in either one of two identified genes known as PIK3CD or PIK3R1, which are vital to the development and function of immune cells. (APDS is also known as PASLI disease.)

People with APDS may suffer from a wide variety of symptoms, most commonly frequent and severe infections of the ears, sinuses, and upper and lower respiratory tracts. Infections usually begin in infancy. APDS patients are also susceptible to swollen lymph nodes or an enlarged spleen (splenomegaly), as well as autoimmunity and inflammatory symptoms. People with APDS may be at higher risk for cancers like lymphoma.

Fast Facts: Activated PI3K Delta Syndrome (APDS)

- The most common symptoms are frequent and severe infections of the ears, sinuses, and upper and lower respiratory tracts
- Infections usually begin in infancy
- People with APDS are susceptible to swollen lymph nodes or an enlarged spleen (splenomegaly), as well as autoimmunity and inflammatory symptoms
- People with APDS may be at higher risk for cancers like lymphoma
- APDS is also known as PASLI disease

Key Signs and Symptoms

Like all primary immunodeficiencies, the symptoms of APDS can vary widely, depending on the patient and the severity of the immune dysfunction. However, there are some relatively clear criteria to help identify people who may have APDS.

Ear, Sinus, and Respiratory Tract Infections
Frequent and severe ear, sinus, and/or respiratory tract infections have been reported to affect 96% to 100% of patients with APDS. Furthermore, 59% to 85% of patients experienced at least one episode of pneumonia.

Enlarged Tonsils, Lymph Nodes, or Spleen Immune cells can build up in certain areas of your body, making them appear enlarged or swollen. This "lymphoproliferation" has occurred in the tonsils, lymph nodes, spleen, and/or liver of 71% to 89% of people with APDS.

Chronic Cough or Difficulty Breathing
Up to 60% of patients with APDS have been reported to have permanent lung damage called bronchiectasis. This results in shortness of breath, coughing up phlegm (mucus), and chest pain.

Gastrointestinal Issues
More than half of people with APDS have been reported to experience digestive tract issues such as bowel inflammation or chronic diarrhea, typically starting around 5 years of age.

Cytopenia
About one-third of people with APDS have reported having low numbers of blood cells (cytopenia) meaning that they have low levels of red blood cells (anemia), white blood cells (leukopenia), or platelets (thrombocytopenia).

Developmental Delays
Speech delay or other neurological conditions have been reported to affect 10% to 31% of people with APDS.

> All through childhood I would get recurring ear infections and would be going to the doctor for antibiotics every month or so.
>
> **-APDS Patient**

The Diagnostic Challenge

Many patients with APDS are undiagnosed, underdiagnosed, or misdiagnosed. A large proportion of patients do not receive an accurate and timely diagnosis, which is crucial for successful management and care of APDS. An unknown number of people living with APDS still remain undiagnosed. The best available estimate is that about 1 to 2 people per million in the United States have APDS, but the actual number is unknown.

Although the diagnostic delay has largely improved over time, there are still many patients in the United States who are needlessly suffering, because they have not yet been accurately diagnosed. Signs and symptoms of APDS can vary from patient to patient and even within a family. Although many individuals will present symptomatology during infancy, typically starting with recurring sinus infections and failure to thrive, these early childhood symptoms are often dismissed [2].

As individuals with APDS grow older through adolescence, the clinical presentation of the condition can change. New symptoms often lead to referrals to multiple medical specialists and the road to diagnosis becomes increasingly complicated to navigate.

Diagnosing all primary immunodeficiencies typically involves a combination of medical history evaluation, physical examination, laboratory tests, and genetic testing. Early diagnosis is crucial for initiating appropriate treatment and preventing complications associated with primary immunodeficiencies. Recent advances in genetic technology have helped significantly in the diagnosis of APDS.

Some common diagnostic tests may include:

- Complete blood count (CBC) to evaluate the levels of different blood cells
- Immunoglobulin levels to assess antibody production
- Flow cytometry to analyze immune cell populations
- Genetic testing to identify specific gene mutations associated with primary immunodeficiencies
- Functional assays to assess immune cell function, such as T cell proliferation or neutrophil oxidative burst tests

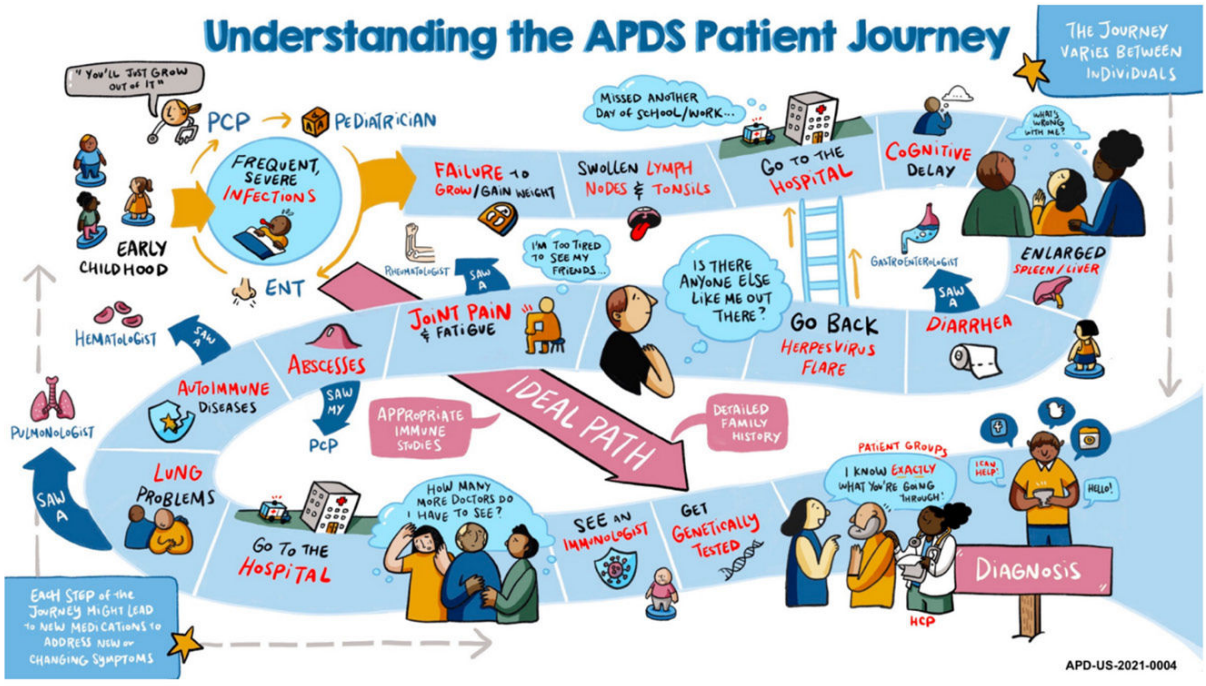
For many individuals with APDS, the journey to diagnosis is long and physically and emotionally damaging. Early genetic testing may lead to a definitive diagnosis of APDS, which can provide individuals with:

- access to current, appropriate symptom management treatments
- referrals to APDS specialists who understand the disease
- opportunities to connect with others around the world with APDS through advocacy and support groups [2]

APDS, like many primary immunodeficiencies, is often investigated by many different specialists, but without appropriate treatment or management. The end result can be deterioration of the patient's condition, inappropriate use of health resources, and a feeling of helplessness [8].

As with many rare diseases, early testing and diagnosis are essential first steps in the care pathway toward timely and appropriate care and treatment, which are ultimately life changing and life enhancing for people living with APDS. The negative consequences of diagnostic delay can include multiple hospital admissions, preventable infections, end-organ damage such as bronchiectasis or hearing loss, and sometimes neurologic problems [3].

> The gold standard for diagnosis of APDS is genetic testing.[2]
>
> **-Jennifer Leiding, MD Pediatric Infectious Diseases & Immunology Orlando Health Arnold Palmer Hospital for Children Infectious Diseases and Immunology**



Understanding the APDS patient journey

This infographic was made by Pharming Healthcare, Inc., based on feedback from patients and caregivers during live interviews and advisory boards [2].

Overall Management of APDS

Managing a primary immunodeficiency like APDS requires a multidisciplinary approach involving healthcare providers, patients, and caregivers. Multiple medical specialists are usually required to help families manage the condition, potentially including:

Immunologists/ Allergists

Pediatricians

Pulmonologists

Otolaryngologists (ENTs)

Infectious Disease Specialists

Hematologists

Rheumatologists

Some key strategies for managing primary immunodeficiencies include:

- Regular follow-up with a primary care physician or immunologist
- Therapy with leniolisib (Joenja), a kinase inhibitor indicated for the treatment of APDS
- Adherence to prescribed treatment regimens, including immunoglobulin replacement therapy, and prophylactic antibiotics
- Maintaining a healthy lifestyle, including proper nutrition, regular exercise, and adequate rest
- Avoiding exposure to known pathogens or infectious agents, such as practicing good hand hygiene and avoiding crowded or poorly ventilated environments
- Seeking prompt medical attention for any signs of infection or illness
- Connecting with support groups or patient advocacy organizations for information, resources, and emotional support

> APDS has impacted my social life greatly. I can't go out as much as I would like to as I get sick easily and it often takes me several weeks to recover.
>
> **-APDS Patient**

New Information About Primary Immunodeficiencies (PIs) and APDS

As scientists learn more about the immune system, more knowledge about primary immunodeficiencies has continued to accumulate. Now there are 485 defined types of primary immunodeficiencies, and many more will be identified in the coming years. Increasing utilization of genetic testing and advances in the strategic evaluation of genetic variants has continued to drive the identification of new PIs. Defining and creating deeper understanding of each condition is the first step. Ongoing research has provided further insights into various aspects of PIDs, including genetics, diagnosis, treatment, and management.

Identification of New Primary Immunodeficiencies:

The number of identified primary immunodeficiencies was approximately 200 in 2010; now it is 485 in 2024. Several PIs have not only been defined, but have been profiled genetically and can be found with genetic testing. For example, in 2013, scientists from NIAID and the National Human Genome Research Institute at the National Institutes of Health identified a novel, genetic human immunodeficiency called APDS (activated phosphoinositide 3-kinase delta syndrome, formerly called PASLI disease). Ten years later, a new drug, leniolisib, designed specifically to treat APDS, was approved by the FDA.

Genetic Discoveries:

Advances in genetic sequencing technologies have facilitated the identification of novel gene mutations associated with PIs. Researchers continue to uncover new genetic variants contributing to different forms of PIDs, expanding our understanding of the genetic basis of these disorders.

Precision Medicine Approaches:

With improved understanding of the genetic basis of PIDs, there's a growing interest in personalized or precision medicine approaches. Tailoring treatment strategies based on an individual's specific genetic mutation or immune profile holds promise for optimizing therapeutic outcomes and minimizing adverse effects.

Gene Therapy and Gene Editing:

Gene therapy and gene editing technologies are being explored as potential treatment modalities for certain PIs. These approaches aim to correct underlying genetic defects in patients' immune cells, offering the possibility of long-term therapeutic benefits.

Novel Therapeutic Targets:

Research efforts are focused on identifying novel therapeutic targets for PIs. This includes exploring the role of various immune pathways and molecules in disease pathogenesis, with the goal of developing targeted therapies that can modulate immune function and mitigate disease manifestations.

Improved Diagnostic Tools:

Advances in diagnostic techniques, such as next-generation sequencing and functional assays, have enhanced the accuracy and efficiency of PI diagnosis. Early and precise diagnosis is crucial for initiating appropriate treatment and improving clinical outcomes in patients with PIs.

Immunomodulatory Therapies:

In addition to conventional treatments such as immunoglobulin replacement therapy and antibiotics, there's growing interest in exploring immunomodulatory therapies for PIDs. These therapies aim to modulate the immune system's function, either by boosting immune responses or suppressing aberrant immune activation, to better control disease activity and prevent complications.

Patient Management and Care Guidelines:

There's an ongoing effort to develop comprehensive management and care guidelines for patients with PIDs. These guidelines encompass various aspects of patient care, including diagnosis, treatment, monitoring, and supportive care measures, with the aim of improving clinical outcomes and quality of life for individuals with PIDs.

Overall, ongoing research efforts continue to advance our understanding of APDS and contribute to the development of novel diagnostic and therapeutic strategies aimed at improving patient outcomes in this challenging immune disorder.

> From the start of symptoms until diagnosis took more than 9 years.
>
> **-APDS Caregiver**

APDS Management: Tips From Caregivers

- You must be your child's (or other patient) advocate - no one else will do it for you
- The healthcare system is not set up for rare conditions like APDS, so you may have to fight for more tests, and then more aggressive treatment
- Work on maintaining overall health - it may sound basic, but making sure that your child eats properly, exercises frequently, and sleeps well are keys to keeping the immune system functioning optimally
- Catch symptoms early - typically the earlier that you notice symptoms of a "flare" and the sooner the treatment, the less severe the flare tends to be
- Lean onto support networks (both in-person and online) - other caregivers have experiences and tips to share, and can help with emotional support

Patient Advocacy Groups

Immune Deficiency Foundation (IDF) - IDF is a national nonprofit organization dedicated to improving the diagnosis, treatment, and quality of life of individuals affected by primary immunodeficiency diseases through advocacy, education, and research.
https://primaryimmune.org

Jeffrey Modell Foundation (JMF) - JMF is a global nonprofit organization dedicated to early diagnosis, meaningful treatments, and ultimately cures for primary immunodeficiency diseases. The foundation provides support, education, and advocacy for patients and families affected by these conditions.
https://info4pi.org

Foundation for Primary Immunodeficiency Diseases (FPID) - Established in the United States to support the education, early diagnosis, genetic counseling, therapy, and research of PID in both India and the United States.
https://fpid.org/wp

Advocacy & Awareness for Immune Disorders Association (AAIDA - Dedicated to patients living with immune dysregulation and overlapping conditions with a focus on advocacy campaigns, educational initiatives, and research opportunities. AAIDA also provides patients and healthcare providers assistance with insurance denials and medication assistance programs available across the United States.
https://www.godoaaida.org

American Partnership for Eosinophilic Disorders (APFED - While not exclusively focused on primary immunodeficiencies, APFED provides support, education, and advocacy for individuals with eosinophilic disorders, which can sometimes occur alongside primary immunodeficiency conditions.
https://apfed.org

Summary

Activated PI3K delta syndrome (APDS) is a recently identified primary immunodeficiency first fully described in 2013. It is a combined immunodeficiency, meaning both B and T cells are affected, and is caused by variants (changes) in one of two genes.

It is a rare genetic immune disorder characterized by overactivity of the PI3K delta enzyme, which plays a crucial role in regulating immune cell function. This overactivity leads to dysregulation of the immune system, resulting in recurrent infections, particularly of the respiratory tract and sinuses, as well as autoimmune complications such as lymphoproliferation and autoimmune cytopenias.

Patients with APDS may also exhibit other symptoms including lymphadenopathy, hepatosplenomegaly, and increased susceptibility to certain cancers. Treatment typically involves managing infections with antibiotics and immunoglobulin replacement therapy, along with targeted therapies to modulate the overactive immune response. Early diagnosis and comprehensive management are essential to improve outcomes and quality of life for individuals with APDS.

When to Talk to Your Physician About Primary Immunodeficiencies or APDS

When you or someone that you care about has:

- Recurrent infections
- Delayed wound healing
- Chronic cough with mucus production
- Difficulty breathing
- Fungal infections/oral thrush
- Delayed growth (in young children)

> Often individuals with APDS will be diagnosed with a host of medical problems but are not aware APDS is the root cause.
>
> **-APDS Patient**

Glossary

Activated PI3K Delta Syndrome (APDS):
A rare primary immunodeficiency that affects approximately 1 to 2 people per million. It occurs when there are variations to the PIK3CD or PIK3R1 genes.

Primary Immunodeficiency (PID):
A group of disorders characterized by defects in the immune system present from birth, leading to increased susceptibility to infections.

Innate Immunity:
The first line of defense against pathogens, involving physical barriers (eg., skin), cellular responses (eg., macrophages, neutrophils), and soluble factors (eg., complement proteins).

Adaptive Immunity:
The immune response mediated by lymphocytes (T and B cells) that specifically targets pathogens and develops memory for future encounters.

T-Cell Deficiency:
A primary immunodeficiency characterized by defects in T lymphocytes, leading to impaired cell-mediated immunity and increased susceptibility to viral, fungal, and certain bacterial infections.

B-Cell Deficiency:
A primary immunodeficiency characterized by defects in B lymphocytes, leading to impaired humoral immunity and increased susceptibility to bacterial infections, particularly encapsulated bacteria.

Combined Immunodeficiency:
A primary immunodeficiency characterized by defects affecting both T and B lymphocytes, leading to severe immunodeficiency and susceptibility to a wide range of infections.

Severe Combined Immunodeficiency (SCID):
A rare and severe form of combined immunodeficiency characterized by profound defects in both T and B lymphocytes, often resulting in life-threatening infections within the first few months of life.

Antibody Deficiency:
A primary immunodeficiency characterized by defects in antibody production, leading to impaired humoral immunity and increased susceptibility to bacterial infections, especially extracellular pathogens.

Common Variable Immunodeficiency (CVID):
A primary immunodeficiency characterized by low levels of serum immunoglobulins (particularly IgG and IgA), leading to recurrent bacterial infections, autoimmune disorders, and an increased risk of malignancy.

Complement Deficiency:
A primary immunodeficiency characterized by defects in components of the complement system, leading to impaired opsonization, chemotaxis, and lysis of pathogens, resulting in increased susceptibility to bacterial infections, particularly *Neisseria* species.

Phagocytic Defects:
A primary immunodeficiency characterized by defects in phagocytes (eg., neutrophils, macrophages), leading to impaired clearance of pathogens and increased susceptibility to bacterial and fungal infections.

Hyper IgM Syndrome:
A primary immunodeficiency characterized by defective class switching of immunoglobulins, resulting in low levels of IgG and IgA but normal or elevated levels of IgM, leading to increased susceptibility to bacterial infections.

X-linked Agammaglobulinemia (XLA:
A primary immunodeficiency caused by mutations in the gene encoding Bruton's tyrosine kinase (BTK), resulting in the absence of mature B cells and low levels of immunoglobulins, leading to recurrent bacterial infections.

Autoimmune Lymphoproliferative Syndrome (ALPS:
A primary immunodeficiency characterized by defective apoptosis of lymphocytes, leading to lymphoproliferation, autoimmune manifestations, and an increased risk of lymphoma.

Hematopoietic Stem Cell Transplantation (HSCT:
A procedure in which hematopoietic stem cells are infused into a patient to restore bone marrow function and immune system competence, often used as a treatment for severe primary immunodeficiencies.

Sources

1. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, Klein C, Morio T, Oksenhendler E, Picard C, Puel A, Puck J, Seppänen MRJ, Somech R, Su HC, Sullivan KE, Torgerson TR, Meyts I. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022 Oct;42(7):1473-1507. doi: 10.1007/s10875-022-01289-3. Epub 2022 Jun 24. PMID: 35748970; PMCID: PMC9244088.

2. Rare Revolution Magazine http://rarerevolutionmagazine.pagesuite.com/digitalspotlight/understanding-the-apds-patient-journey

3. IPOPI. Tackling Diagnostic Odyssey in Rare Diseases Through ERNs: The Case of PIDs. (2017). Available from: https://ipopi.org/wp-content/uploads/2017/12/IPOPI-Recommendations-on-ERNs-to-enhance-PID-diagnosis.pdf

4. Hariyan T, Kinash M, Kovalenko R, Boyarchuk O (2020) Evaluation of awareness about primary immunodeficiencies among physicians before and after implementation of the educational program: A longitudinal study. PLoS ONE 15(5): e0233342. https://doi.org/10.1371/journal.pone.0233342

5. Modell, V., Orange, J.S., Quinn, J. et al. Global report on primary immunodeficiencies: 2018 update from the Jeffrey Modell Centers Network on disease classification, regional trends, treatment modalities, and physician reported outcomes. Immunol Res 66, 367–380 (2018). https://doi.org/10.1007/s12026-018-8996-5

6. Anderson JT, Cowan J, Condino-Neto A, Levy D, Prusty S. Health-related quality of life in primary immunodeficiencies: Impact of delayed diagnosis and treatment burden. Clin Immunol. 2022 Mar;236:108931. doi: 10.1016/j.clim.2022.108931. Epub 2022 Jan 19. PMID: 35063670.

7. Gumusburun R, Altay S, Cengiz H, Hakverdioglu Yont G, Kuman Tuncel O, Ardeniz O. Psychosocial Evaluation of Adults with Primary Immunodeficiency. J Clin Immunol. 2024 Feb 27;44(3):71. doi: 10.1007/s10875-024-01671-3. PMID: 38411715; PMCID: PMC10899353.

8. Chapel H, Prevot J, Gaspar HB, Español T, Bonilla FA, Solis L, Drabwell J; Editorial Board for Working Party on Principles of Care at IPOPI. Primary immune deficiencies - principles of care. Front Immunol. 2014 Dec 15;5:627. doi: 10.3389/fimmu.2014.00627. PMID: 25566243; PMCID: PMC4266088.