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REVIEW ARTICLE

An updated review on activated PI3 kinase delta syndrome (APDS)

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Abstract Activated Phosphoinositide 3-kinase δ syndrome (APDS) is a newly recognised primary immunodeficiency disease. It has currently been a hot topic of clinical research and new data are emerging regarding its pathogenesis, clinical manifestations and treatment. Patients with APDS syndrome have significant autoimmune manifestations and lymphoproliferation. It is important to differentiate APDS from the usual polygenic CVID in view of the availability of targeted therapy like mTOR inhibitors such as Rapamycin and selective PI3Kδ inhibitors. We provide a comprehensive review on this interesting disorder focusing light on its etiology, genetic research and emerging therapy.

Background

Activated Phosphoinositide 3-kinase δ syndrome (APDS) is a recently recognised primary immunodeficiency disease. APDS is caused by gain of function (GOF) mutation in the *PIK3CD* gene that encodes for p110δ catalytic subunit of Phosphoinositide 3-kinase δ (PI3Kδ) (APDS1). A similar syndrome caused by a mutation in the *PIK3R1*gene that encodes for p85α regulatory subunit of *PI3Kδ* has also been described (APDS2).[1,2] The encoded protein is predominantly expressed in leukocytes and plays a prominent role in survival, proliferation and activation.[3] Clinically, this syndrome resembles common variable immunodeficiency (CVID), but in addition to CVID, clinical features of cellular immunodeficiency are evident along with autoimmunity.

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Therefore, APDS is a combined immunedeficiency. APDS has also been named as "p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency" (PASLI disease).

Pathogenesis and genetics of APDS

The Phosphoinositide 3-kinases (PI3Ks) belong to family of kinases that have an important role in intracellular signaling in various mammalian cells. PI3Ks consists of three different classes viz. PI3Kα, PI3Kβ, and PI3Kδ. Each class of PI3K consists of 3 catalytic subunits and 5 regulatory subunits. It acts downstream of various cytokine receptors, T cell receptors (TCRs), B cell receptors (BCR) and Toll-like receptors (TLRs). It is also involved in cellular functions like proliferation, trafficking, differentiation and survival.[4,5] PI3Kδ consists of catalytic subunits (p110α, p110β and p110δ encoded by *PIK3CA*, *PIK3CB* and *PIK3CD* respectively) and regulatory subunits (p85α, p55α, p50α, p85β, p55γ). Among the regulatory subunits p85α, p55α, p50α are encoded by *PIK3R1* while p85β, p55γ are encoded by the *PIK3R2* and *PIK3R3* respectively.

Both p85α and p110δ are included in class IA PI3Ks. They play an important role in the development, differentiation and functions of different stages of T and B lymphocytes.[4,5] The p110δ catalytic subunit encoded by *PIK3CD* gene is expressed predominantly in hematopoietic stem cells, lymphocyte and myeloid cells. Gain of function mutations in *PIK3CD* gene leads to hyperactivity of PI3Kδ and senescence of the effector T cells. These variants thus lead to activating PI3Kδ syndrome (APDS type I). Mutations in *PIK3R1*gene, regulatory subunit encoding p85α, p55α, p50α units leads to APDS Type 2 or PASLI-R1.

Mechanism of autoimmunity and lymphoproliferation in patients with APDS

Activation of receptor tyrosine kinases (RTK) recruits certain adaptors (viz. Gab2 or IRS family proteins) that attach to the p85 subunit (regulatory subunit) of PI3K and lead to activation of catalytic p110α, β, δ subunits of PI3K. PI3Kδ converts phosphatidylinositol 4,5-biphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3) which recruits PDK1, PDK2 (mTORC2) and AKT (AKT Serine/Threonine Kinase 1) to the plasma membrane. Phosphorylation of AKT is carried out by PDK1 on Thr308 and by PDK2 on Ser473[4,5](Fig. 1). This leads to further up-regulation of mTOR signaling pathway and increased production of transcription factors, FOXO (FOXO1, FOXO3A, FOXO4). These transcription factors enter the nucleus and cause transcription of genes such as CDN1A ($p21^{Cip1}$), CDN1B ($p27^{Kip1}$), Fas-L (TNFL6) and BIM, which are involved in process of apoptosis and regulation of cell cycle.[6] Dysregulation of this pathway as seen in patients with APDS leading to autoimmunity and lymphoproliferation.

Inheritance pattern

APDS is a genetic disease that follows an autosomal dominant mode of inheritence. Recent literature has also suggested the role of paternal gonadal mosaicism in the inheritance of activated PI3-kinase delta syndrome.[7]

Genes involved in PI3K/AKT signaling

The structure of the *PIK3CD* and *PIK3R1*genes consists of various domains such as RBD (Ras-binding domain); ABD (adaptor-binding domain); P (proline-rich regions); BH (breakpoint cluster region homology domain). Certain newly identified mutations in the linker between RBD and ABD alter the orientation of ABD and thus affect the interaction between translated proteins.[8] The different domains of the *PIK3CD* and *PIK3R1* genes are illustrated in Figs. 2 and 3 respectively.

Genetic variants in patients with APDS

Genetic variation in these genes involved in the PI3K/AKT pathway leads to hyperactive PI3K/AKT signaling. Increased downstream signaling caused by germline gain-of-function

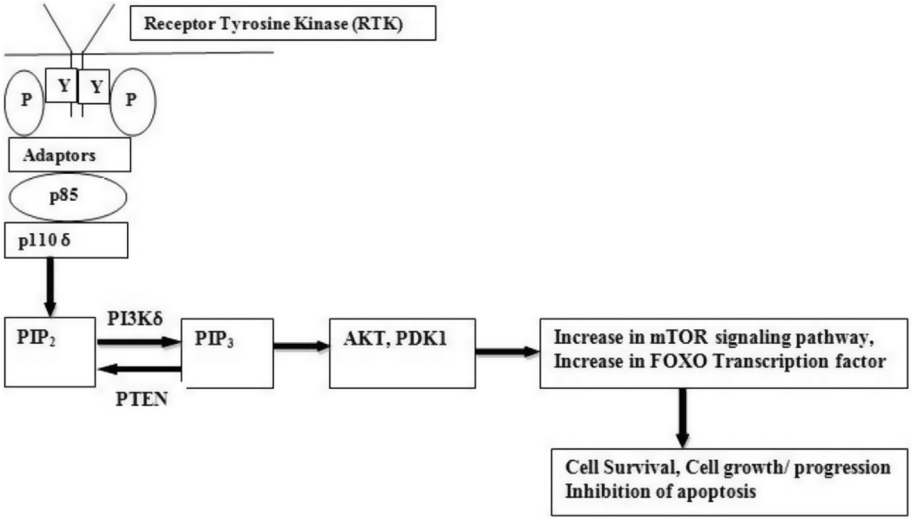

Figure 1 Phosphoinositide-3-kinase (PI3K) signaling pathway.

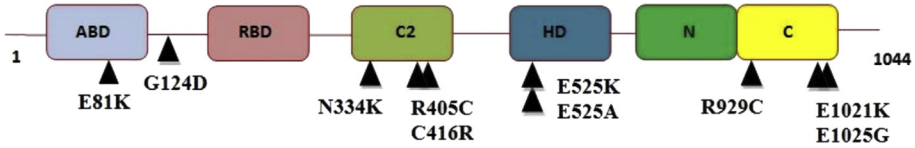

Figure 2 Domains of *PIK3CD* gene and previously reported pathogenic variants in its various domains.

Figure 3 Domains of *PIK3R1* gene and previously reported pathogenic variants in its various domains.

mutations leads to many clinical presentations (lymphoproliferation, autoimmunity and senescence of CD8+ T cells). Some of these mutations lead to truncation of p85α domain thereby leading to failure of interaction between catalytic and regulatory subunits and causing hyperactivation of catalytic subunit (p110δ). Several pathogenic variants in these 2 genes that have been reported till date are described in Table 1.[1,2,9–20,21–37] The most common reported variant in the *PIK3CD* gene is E1021K. It enhances membrane association and activity of p110δ. Mutation in *PIK3CD* gene may cause Hyper IgM syndrome like phenotype as well as in some cases increase the susceptibility to cancer.[12] One of the reason of these abnormal phenotypes is defective signaling through PI3K/AKT pathway.[6]

Patients with this mutation have also been demonstrated to have elevated levels of phosphorylated AKT protein and PIP3 in the lymphocytes and these were susceptible to activation-induced cell death.

Tsujita et al have recently reported 2 patients with loss of function mutation in *PTEN* gene with clinical and immunological features reminiscent of APDS. They demonstrated increased signaling of AKT/mTOR/S6 in lymphocytes of these patients that could have lead to this phenotype.[13]

Clinical manifestations of APDS

Clinical presentations in patients with APDS may range from severe infections and lymphoproliferation in early age group to an asymptomatic adult patient. The clinical phenotype of patients with APDS is summarized in Fig. 4.

Many of these clinical manifestations are similar to those seen in patients with monogenic forms of common variable immunodeficiency such as Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and Lipopolysaccharide responsive and beige-like anchor protein (LRBA) deficiency. In the largest series of 53 patients reported till date, recurrent respiratory tract infections (pneumonia followed by otitis media and rhinosinusitis) were the most common clinical manifestations. Bacterial infections were most commonly caused by *Haemophilus influenza* and *Streptococcus pneumoniae*, similar to that seen in patients with antibody

Table 1 Mutations reported in *PIK3CD* (APDS1) and *PIK3R1* (APDS2) genes.

Gene	S. No.	cDNA position	Codon change	References
PIK3CD	1.	c.241; G > A	p.E81K	15,16
	2.	c.371; G > A	p.G124D	15,16
	3.	c.1002; C > A	p.N334K	2,19
	4.	c.1213; C > T	p.R405C	17
	5.	c.1246; T > C	p.C416R	12
	6.	c.1573; G > A	p.E525K	2,18,19,26
	7.	c.1574; A > C	p.E525A	13
	8.	c.2784; C > T	p.R929C	18
	9.	c.3061; G > A	p.E1021K	1,2,9,12,13,18,19,26,32,33,35,40,42,43,44,45,51,53
	10.	c.3073; A > G	p.E1025G	19
PIK3R1	1.	c.1692; C > G	p.N564K	18
	2.	c.1425 + 1; G > C	delE11 (del434-475)	10,11,33
	3.	c.1425 + 1; G > A	delE11 (del434-475)	11,46,48,50
	4.	c.1425 + 1; G > T	delE11 (del434-475)	10,33,47,52
	5.	c.1300−1; G> C c.1425 + 2; T > A c.1425 + 2; T > G (c.1425 + 2); TG > del	delE11 (del434-475)	14,49
	6.	c.1425 + 2; A > T	delE11 (del434-475)	18
	7.	c.1418_1425+1del	delE11 (del434-475)	41

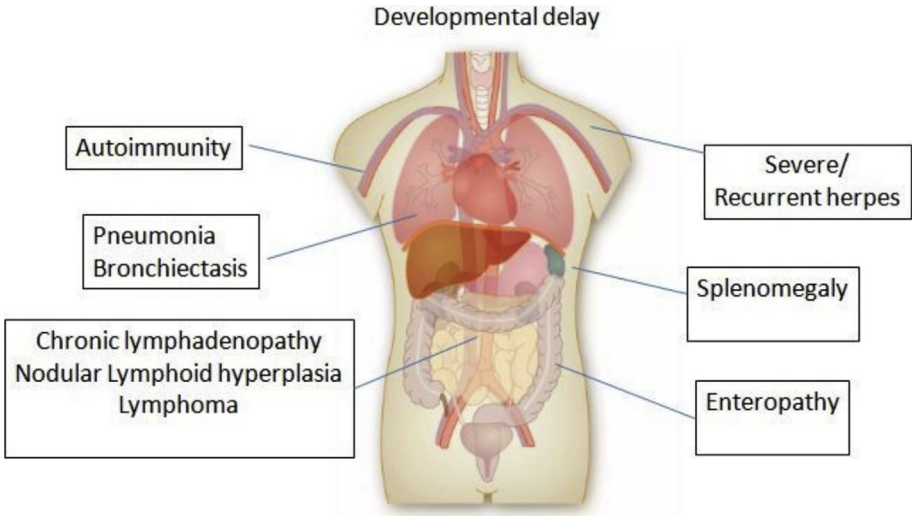

Figure 4 Clinical features in patients with APDS.

deficiencies.[38,39] Other less common pathogens isolated were *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis and Klebsiella* sp. Recurrent respiratory tract infections led to bronchiectasis in more than half of these patients. Invasive bacterial infections are not commonly seen in these patients.

In addition, approximately half of these patients often have chronic non-resolving infections with herpes group of viruses e.g. Epstein—Barr virus (EBV), cytomegalovirus (CMV) and herpes simplex virus (HSV). Susceptibility to EBV and other herpes virus infections in patients with APDS is intriguing as viral infections are typically seen with loss of function mutations and defect in cell-mediated immunity. However, the exact mechanism of susceptibility to viral infections in patients with APDS has not been clearly defined but various theories have been proposed. PI3K pathway plays an essential role in protection against herpes virus infections. It is involved both in maintaining their latency and in reactivation of viruses.[40] One of the proposed mechanism is related to dysregulation in B cell function and differentiation.[41] The role of neutralizing antibodies in providing protection against EBV is now emerging.[42] The transitional B cells may be the entry point for EBV in these patients and act as reservoir for EBV.[43] Studies have also

Table 2 Immunological investigations in APDS.

Immunological parameters	Result
Serum IgG	Low to normal
Serum IgA	Low to normal
Serum IgM	Normal to elevated
Ig G subclasses	Normal to decreased
Anti-polysaccharide Ab response	Normal to diminished
Anti-peptide Ab response	Normal to diminished
CD3+ T lymphocytes	Decreased
CD19 + B lymphocytes	Decreased
CD3- CD16 + 56+ Natural killer (NK) cells	Normal to decreased
CD3+CD4+ (Helper T lymphocytes)	Decreased
CD3+CD8+ (Cytotoxic T lymphocytes)	Normal to Increased
CD4/CD8 ratio	Reversed
CD3+ CD4/CD8+ CD45RA+ (Naïve T lymphocytes)	Decreased
CD3+ CD4/CD8+ CD45RO+ (Memory T lymphocytes)	Normal
CD3+ CD8+ CCR7- CD45RA+ (Effector Cytotoxic T lymphocytes)	Increased
CD3+ CD8+ CCR7- CD45RA- (Effector Memory Cytotoxic T lymphocytes)	Increased
CD3+ CD4+ CD25high FoxP3+ (Regulatory T lymphocytes)	Increased
CD3+ CD4/CD8+ CD57+ (Senescent T cells)	Increased
lCD19 + $CD27^{int}$CD38++IgM++ (Transitional B lymphocytes)	Increased
CD19 + CD27−IgM + IgD+ (Naïve B lymphocytes)	Decreased
CD19 + CD27 + IgM++IgD+ (Marginal zone-like B lymphocytes)	Decreased
CD19 + CD27 + IgM + IgD+ (Unswitched memory B lymphocytes)	Normal to decreased
CD19 + CD27 + IgM−IgD− (Switched memory B lymphocytes)	Normal to Decreased

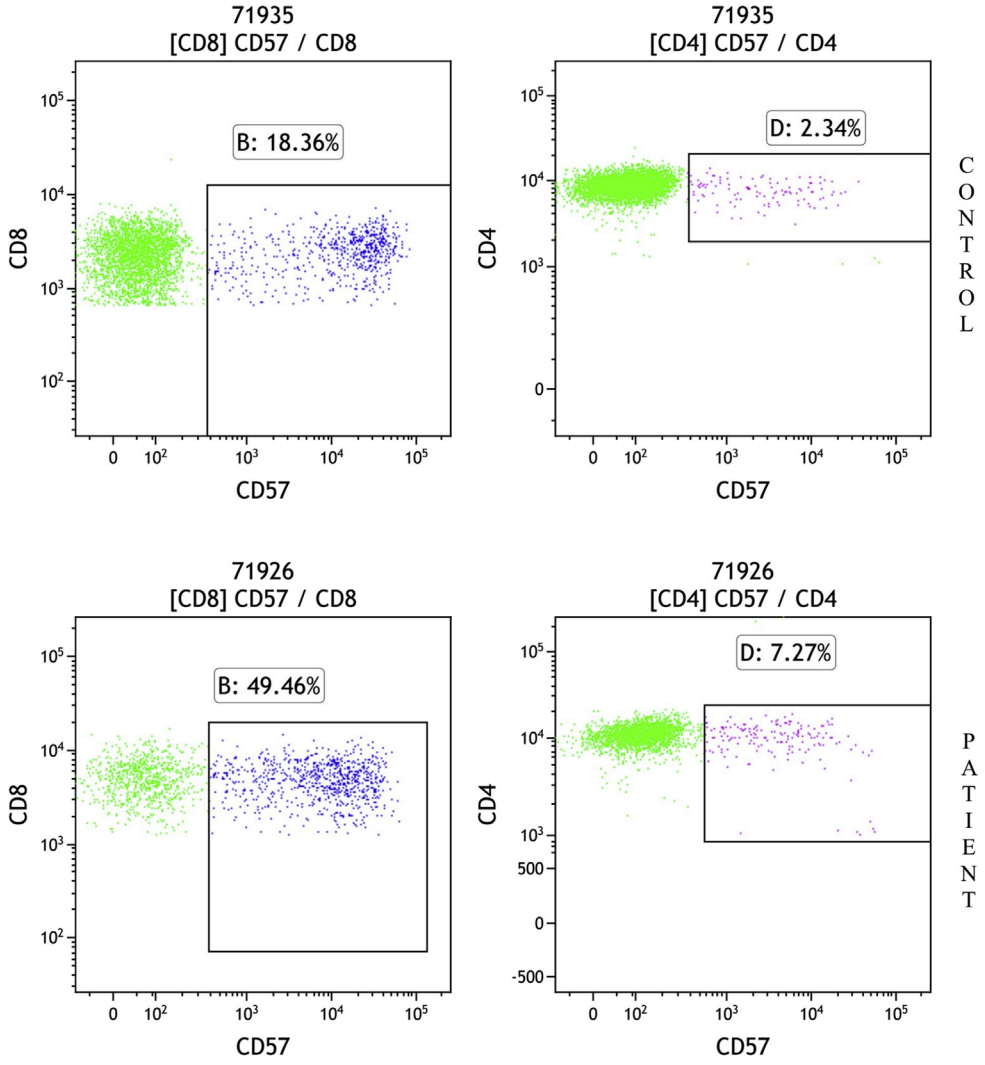

Figure 5 CD57 profile of a patient with APDS using flow cytometry.

demonstrated that decreased PI3K activity leads to reduced EBV reactivation and increased PI3K activity seen in patients with APDS which may increase the chances of reactivation of EBV. Another mechanism involving cytotoxic T cells has also been proposed as seen in patients with X-linked lymphoproliferative (XLP) syndrome. However, patients with APDS do not show increased risk of HLH probably because hyperactive PI3K T cell prevents development of cytokine storm. Though, there is expansion of effector CD8+ T cells in APDS, these are terminally differentiated and show characteristics of senescence. This immunosenescence may be responsible for defective response of CD8+ T cells to EBV.

Other infections that have been reported uncommonly in these patients include *Cryptosporidium* sp. and Bacillus Calmette-Guerin (BCG).[34] Granulomatous inflammation at the site of BCG vaccination was reported in 1 patient.

Chronic non-malignant lymphoproliferation (in the form of generalized lymphadenopathy and hepatosplenomegaly) is a common feature seen in approximately 3/4th of all patients. Histological examination of lymph nodes reveals an absence or attenuation of follicular mantle zones. Germinal centers are disrupted by follicular helper T cells. Another important feature is aggregation of monocytotic B cells in parasinusoidal space. Few patients have lymphoproliferative findings similar to posttransplant patients with a polymorphic infiltrate consisting of T and B cells, plasma cells and epithelioid macrophages. Some patients may show CMV or EBV positive cells in lymph nodes but this is different from florid infectious mononucleosis.

Other than a few reports of candida infection in patients with APDS, invasive fungal infection are not commonly seen.

Autoimmune manifestations (predominantly cytopenias and glomerulonephritis) have also been commonly reported in approximately 1/3rd of these patients.[8,44]

Patients with APDS have increased risk of lymphoma. Both Hodgkin and Non-hodgkin lymphoma have been reported in these patients. The incidence of lymphoma reported is as high as 13% and many of them had underlying EBV-infection.[34]

Neurodevelopmental abnormalities such as speech delay and global developmental delay have been reported in patients with APDS. Pervasive developmental disorders are more commonly reported in patients with APDS2.[8] Patients

with APDS, especially APDS2, commonly have growth retardation.

Laboratory investigations

The overview of immunological abnormalities observed in patients with APDS is given in Table 2[12,34,45]

Senescent T-cells (CD57 + CD3+) particularly are often increased in patients with APDS and are one of the characteristic laboratory manifestations of APDS (Fig. 5).[2] These cells also tend to improve with treatment.

Hyperactive PI3K signaling is characteristic of patients with APDS. Phosphorylated AKT can be used as a marker for performing functional studies in these patients.[46]

Senescent cells are characterized by shortening of telomeres. Shortened telomeres on total lymphocytes have been reported previously in an old patient with APDS[11] as well as in a young patient with APDS. Naïve CD8+ T cells from patients with APDS had shortened absolute telomere lengths when compared to those from age-matched controls.

Sequencing of the genes of PI3K/AKT pathway especially *PIK3CD* and *PIK3R1* could lead to definitive diagnosis of patients with APDS.

Management options

As the clinical profile of patients with APDS varies in spectrum from mildest forms to severe life threatening manifestations, the therapeutic options may also vary from simple observation to hematopoietic stem cell transplantation (HSCT).

Since the infection profile is similar to antibody deficiencies, the antimicrobial agents used for prophylaxis are also the same. The most commonly used agents are trimethoprim/sulfamethoxazole and azithromycin. This alone may be sufficient in few patients.

As these patients can have defect in antibody production and functions, most studies have shown response to Immunoglobulin replacement therapy (IRT).[34,14] It can be given either by intravenous (IVIG) or subcutaneous (SCIG) route. Usual dose of IVIG is 0.4 g/kg/month. In presence of bronchiectasis, dose can be increased to 0.6 g/kg/month.[47,48] It is beneficial in decreasing recurrent respiratory infections, however it may not be of much aid in preventing herpes infections, autoimmunity and lymphoproliferation.[14,35]

HSCT has been useful to treat lymphomas and life threatening infections in these patients.[34] There is paucity of data but most reported studies have shown good response to HSCT.[36] However, data on long term follow-up of these patients who have been transplanted is still lacking.[49]

Immuno-modulatory therapy is useful in presence of clinical features of autoimmunity eg. cytopenias, renal disease, arthritis, inflammatory colitis, sclerosing cholangitis etc. Autoimmune cytopenias have been managed with steroids, rituximab and splenectomy.[12,39] Liver transplant has also been performed in patients with sclerosing cholangitis[37]. Rituximab was also useful in non-neoplastic lymphoproliferation.[39]

Sirolimus (Rapamycin) is inhibitor of mTOR, that is involved in T cell metabolism and immune regulation.[50] It has been found useful to decrease hepatosplenomegaly, lymphadenopathy, restore T cell proliferation and treat non-neoplastic lymphoproliferation. Response is less satisfactory for cytopenias and gastrointestinal symptoms.[2,51]

Selective PI3 kinase inhibitors such as Leniolisib and Nemiralisib are being studied in clinical trials for the treatment of adult patients with APDS. Preliminary results have shown good response in lymphoproliferation, overall well-being and immunological parameters.[52,53]

Conclusion

APDS is indeed an intriguing disease with features of both primary immunodeficiency and autoimmune inflammation. Studies in understanding the detailed pathogenesis of this disease will play an important role to create new horizons in its diagnosis and management.

Conflict of interest

The authors declare no conflict of interest.

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