



Clinical, Immunological, and Genetic Features in Patients with Activated PI3K δ Syndrome (APDS): a Systematic Review

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Abstract

Activated phosphoinositide 3-kinase delta syndrome (APDS) is a novel primary immunodeficiency (PID) caused by heterozygous gain of function mutations in PI3K δ catalytic p110 δ (*PIK3CD*) or regulatory p85 α (*PIK3R1*) subunits leading to APDS1 and APDS2, respectively. Patients with APDS present a spectrum of clinical manifestations, particularly recurrent respiratory infections and lymphoproliferation. We searched PubMed, Web of Science, and Scopus databases for APDS patients and screened for eligibility criteria. A total of 243 APDS patients were identified from 55 articles. For all patients, demographic, clinical, immunologic, and molecular data were collected. Overall, 179 APDS1 and 64 APDS2 patients were identified. The most common clinical manifestations were respiratory tract infections (pneumonia (43.6%), otitis media (28.8%), and sinusitis (25.9%)), lymphoproliferation (70.4%), autoimmunity (28%), enteropathy (26.7%), failure to thrive (20.6%), and malignancy (12.8%). The predominant immunologic phenotype was hyper-IgM syndrome (48.1%). Immunologic profiling showed decreased B cells in 74.8% and CD4⁺ T cells in 64.8% of APDS patients. The c.3061 G>A (p. E1021K) mutation in APDS1 with 85% frequency and c.1425+1 G>(A, C, T) (p.434–475del) mutation in APDS2 with 79% frequency were hotspot mutations. The majority of APDS patients were placed on long-term immunoglobulin replacement therapy. Immunosuppressive agents such as rituximab, tacrolimus, rapamycin, and leniolisib were also administered for autoimmunity and inflammatory complications. In addition, hematopoietic stem cell transplantation (HSCT) was used in 12.8% of patients. APDS has heterogynous clinical manifestations. It should be suspected in patients with history of recurrent respiratory infections, lymphoproliferation, and raised IgM levels. Moreover, HSCT should be considered in patients with severe and complicated clinical manifestations with no or insufficient response to the conventional therapies.

Keywords APDS · Activated phosphoinositide 3-kinase δ syndrome · Phosphoinositide-3-kinase δ · Hyper-IgM syndrome

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Introduction

Activated phosphoinositide 3-kinase delta syndrome (APDS) is a recently described primary immunodeficiency (PID) caused by autosomal dominant mutations that increase the activity of the phosphoinositide-3-kinase δ (PI3K δ) pathway [1, 2]. APDS can be caused by mutations in the *PIK3CD* gene encoding the p110 δ catalytic subunit of PI3K δ (APDS1) [1, 2] or the *PIK3R1* gene that encodes the p85 α regulatory subunit of PI3K δ (APDS2) [3, 4]. Since its first description in 2013, the rapidly increasing number of identified patients indicates that this disorder is a significant cause of primary antibody deficiency (PAD), which should be considered in patients presenting with atypical and severe complications [5].

APDS is clinically heterogeneous and characterized by the early occurrence of recurrent respiratory tract infections, lymphoproliferation, gastrointestinal manifestations, autoimmunity, and increased risk of malignancy [6]. Although most manifestations occurred in the pediatric age, adult-onset and asymptomatic courses were also reported [7]. The immunological phenotypes of APDS patients are also heterogeneous with both B and T cell abnormalities. B cell compartment abnormalities consist of mild B cell lymphopenia, increased transitional B cells, decreased class switched memory B cells and class-switch-recombination defects (CSR-D). Elevated IgM levels have been reported in most of the patients while total IgG and IgA levels can be either normal or markedly decreased. A reduction of naïve CD4⁺ and CD8⁺ T cell numbers with increased frequency of effector memory CD8⁺ T cells and inverted CD4⁺/CD8⁺ T cell ratio was also reported [7–9].

Considering the increasing number of identified APDS patients and its heterogeneous manifestations, we here aim to systematically summarize and evaluate the existing experience of APDS patients in terms of clinical, immunological, and genetic features.

Materials and Methods

Search Strategy

A comprehensive search limited to English language was performed using PubMed, Web of Science, and Scopus databases applying the following search terms: “APDS,” “Activated PI3K Delta Syndrome,” “Activated PI3K δ syndrome,” “Activated Phosphoinositide 3 kinase Delta syndrome,” “Activated Phosphoinositide 3 kinase δ syndrome,” “*PIK3CD* mutation,” and “*PIK3R1* mutation” in various combinations. The search was conducted using these terms in the keywords, titles, and abstracts. Reference lists of all full-text articles and major reviews were hand-searched for additional studies.

Study Selection

The articles were first screened based on the title and abstract to exclude all irrelevant studies and were classified into three categories (include, exclude, or “unclear”); the full-text version of all “unclear” articles was checked and subsequently classified in one of the two categories (include or exclude). All full-text manuscripts were assessed for eligibility criteria: written in English; published in the 2013–2018 period; conducted on human subjects; report of at least one patient with APDS diagnosis; and detailed description of epidemiological, clinical, and immunological features. Studies using animal models, reviews, congress abstracts, and articles in languages other than English were excluded. When necessary, the corresponding authors were contacted.

Data Extraction

In a first step, two researchers extracted the data from all included studies based on the manuscript titles and abstracts. The following data were collected from all identified studies: name of the first author; publication year; number of participants; and demographic, clinical, laboratory, and molecular data. The evaluation of immunologic data quality was based on the age-matched normal ranges included in each article.

Those patients appearing in more than one publication were identified, and overlapping data was deleted. Two reviewers performed the selection process independently, while the third reviewer was consulted to resolve disagreements between two reviewers.

Statistical Analysis

Aggregate data analysis was performed with simple data pooling. By this, an overall summary of subgroup data or data from a number of related studies were combined without weighting. Central and descriptive statistics were reported for quantitative data. For variables with abnormal distribution, median and interquartile ranges (IQR) were calculated. For group comparisons, *U* Mann–Whitney, chi-square, or Fisher exact tests were applied. A *p* value < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS software (v. 25.0, Chicago, IL).

Results

Study Characteristics

The literature search identified a total of 2763 articles. Four hundred and eighty-one articles were duplicated, and 2222 articles were excluded following title and abstract screening. Furthermore, five articles were excluded as they only reported

general information regarding APDS patients lacking specific details. As shown in Figure S1, 55 articles fulfilled the inclusion criteria and were subsequently used for data extraction. The total of 292 APDS patients were reported in these 55 articles, and after the removal of duplicate cases, 243 patients remained for data analysis.

Epidemiologic Characteristics of APDS Patients

In this systematic review, we evaluated 243 APDS patients (123 males, 87 females, and 33 unknown gender). The median (IQR) age of diagnosis was 12.0 (6.5–21.5) years with a median (IQR) diagnostic delay of 7.0 (3.4–14.0) years. A positive family history of immunodeficiency was reported in 88 cases (38.6%). Demographic data of all patients are summarized in Table 1. For 103 patients, information regarding their life status was available. Of these, 89 patients (87.9%) are currently alive and 14 (12.1%) have deceased. Malignancies (e.g., lymphoma, and acute myeloid leukemia), cardiopulmonary arrest, bowel perforation, septic shock, multiple organ failure, and pulmonary hemorrhage were the reported causes of death. Infections occurred early in life (<1 year), while enteropathy, lymphoproliferation, autoimmunity, and malignancy occurred at the median (range) age of 5.0 (1.1–18.0), 3.0 (1.0–6.0), 10.5 (6.0–15.0), and 18.0 (13.2–24.2) years, respectively.

Clinical Spectrum of APDS Patients

Among patients with an established primary diagnosis ($n = 39$), most patients were diagnosed initially with hyper-IgM (HIGM) syndrome ($n = 11$, 28.2%) or lymphoma ($n = 8$, 20.5%). Figure 1 shows the wide range of initial clinical diagnosis of APDS patients. As illustrated in Fig. 2, respiratory tract infections (65%) were the most common first presentation in APDS patients followed by organomegaly (15.8%).

Infective Complications

Upper respiratory tract infections (sinusitis (25.9%) and otitis (28.8%)), pneumonia (43.6%), diarrhea (16%), and eye infections (10.7%) were the most common infectious manifestations in APDS patients. Sinusitis was significantly more common in APDS1 ($p = 0.028$), while pneumonia and eye infection were more frequently reported in APDS2 patients ($p < 0.001$, and $p = 0.004$, respectively) (Table 2).

Pathogenic Organisms

The most common infection-causing agents identified in APDS patients were viruses (*Epstein–Barr virus (EBV)*, *cytomegalovirus (CMV)*, *Varicella zoster virus (VZV)*, and *Human papillomavirus* reported in 28.1%, 14.7%, 6.9%, and

5.6% of patients, respectively), bacteria (*Streptococcus pneumoniae* (12.1%), *Haemophilus influenza* (10.4%) and *Staphylococcus aureus* (1.7%)), and fungal pathogens (*Candida albicans* (6.5%)). In general, *Streptococcus pneumoniae* and *Haemophilus influenza* were significantly more frequent in APDS1 than in APDS2 ($p = 0.002$ and $p = 0.005$, respectively) (Table S1).

Non-infective Complications

Non-neoplastic Lymphoproliferation Among patients with lymphoproliferative diseases, lymphadenopathy was the most frequent manifestation (58.4%), followed by splenomegaly (43.7%) and hepatomegaly (24.2%). As illustrated in Table 2, lymphadenopathy was more common in APDS2, whereas hepatomegaly was reported more frequently in APDS1 patients ($p = 0.004$ and $p = 0.001$, respectively). Benign lymphoid proliferations including reactive hyperplasia and lymphadenitis in the gastrointestinal and respiratory tract were reported in 60 (24.7%) patients and more frequently in APDS1 patients ($p < 0.001$). Tonsillar hypertrophy was observed in 21 (8.6%) patients with a predominant representation of APDS2 patients ($p < 0.001$).

Autoimmune and Inflammatory Disease A variety of autoimmune conditions, including hematological, rheumatologic, gastrointestinal, endocrine, and dermatologic disorders, were reported in about one-fourth of patients (28%). As shown in Fig. 3, autoimmune hematologic disorders including autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP) were the most frequent autoimmune complications (76.2%) among reported autoimmunity conditions. Figure 3 also illustrates the coexistence of different autoimmune diseases in APDS, as 6.5% of patients had multiorgan autoimmunity. Enteropathy was reported in 26.7% of APDS patients, and it was more frequent in APDS1 (28.5%) than APDS2 (21.9%); although, this difference was not statistically significant.

Malignancies Thirty-one patients (12.8%) developed malignant diseases (Table S2) with a median age of onset of 18.0 years (range, 13.2–24.2 years). Diffuse large B cell lymphoma (DLBCL) was diagnosed in 14 (5.7%), classical Hodgkin lymphoma (CHL) in 9 (3.7%), and marginal zone B cell lymphoma in 5 (2.0%) patients. Among patients with malignancy, 8 (25.8%) patients had multiple lymphomas. The frequency of malignancy was higher in patients with a history of (chronic) viral infections than those without previous viral infections (19.5% vs. 7.4%, $p = 0.006$). Sixty-seven patients (27.6%) had a positive EBV infection history, and among these, 12 patients (17.9%) developed a lymphoma. EBV infection was reported in about half ($n = 12$, 44.4%) of the patients who developed lymphoma ($n = 27$, 11.1%). The

Table 1 Demographic data of patients with APDS

Parameters	Total	APDS1	APDS2	<i>p</i> value
Sex ratio, M/F, (<i>n</i> = 210)	123/87	103/69	20/18	0.411
Family history of PID, (<i>n</i> = 228)	88 (38.6)	69 (42.1)	19 (29.7)	0.084
Dead, % (<i>n</i> = 116)	14 (12.1)	7 (10.1)	7 (14.9)	0.441
Current age, years, median (IQR) (<i>n</i> = 213)	12.0 (6.5–21.5)	13 (8–23)	7 (4.7–16.7)	0.002*
Age at onset, years, median (IQR), (<i>n</i> = 111)	1.66 (0.58–3.0)	1.16 (0.5–2.5)	2 (0.78–5)	0.046*
Age at diagnosis, years, median (IQR), (<i>n</i> = 67)	10.0 (5.0–19.0)	9.5 (6.0–14.7)	15 (4.5–22.0)	0.765
Delay in diagnosis, years, median (IQR), (<i>n</i> = 55)	7.0 (3.4–14.0)	6.8 (4.0–13.0)	8.5 (3.1–16.2)	0.737
Age at presentation of infection, years, median (IQR), (<i>n</i> = 36)	1.16 (0.62–2.0)	1.4 (0.8–2.0)	1 (0.37–2.0)	0.574
Age at presentation of autoimmunity, years, median (min-max), (<i>n</i> = 2)	10.54 (6.0–15.0)	6.0	15.0	0.317
Age at presentation of enteropathy, years, median (IQR), (<i>n</i> = 5)	5.0 (1.08–18.0)	3.5 (0.6–13.2)	20	0.157
Age at presentation of non-neoplastic lymphoproliferation, years, median (IQR), (<i>n</i> = 20)	3.0 (1.0–6.0)	1.0 (1.0–3.0)	6.0 (3.0–15.5)	0.002*
Age at presentation of Malignancy, years, median (IQR), (<i>n</i> = 34)	18 (13.25–24.25)	16.5 (12.5–19.25)	19.5 (13.2–27.7)	0.501

The median is shown (with 25th and 75th percentiles)

M male, F female, N count, Y year

**p* value is statistically significant < 0.05

lymphoma risk was significantly higher in patients with a previous EBV infection history (17.9% vs. 8.5%, *p* = 0.037).

Other Complications Bronchiectasis was the most common structural complication in 28.4% of patients, and history of recurrent pneumonia was reported in about half of these patients (52.2%). Despite the observed higher frequency of pneumonia in APDS2, bronchiectasis was more common in APDS1 than in APDS2 patients (*p* = 0.001).

Failure to thrive was reported in 20.6% and was significantly more prevalent in APDS2 when compared to APDS1 (51.6% vs. 9.5%, *p* < 0.001). Ear nose and throat problems (e.g., adenoid and tonsillar hypertrophy, otitis, hearing

impairment, parotitis) were observed in 35.7% of APDS individuals. Neurologic/learning disorders were repeatedly reported in APDS patients (14%) and were significantly more frequent in those with APDS2 mutations (*p* = 0.001).

Immunological Findings of APDS Patients

Immunological data is summarized in Table 3. Of the evaluated APDS patients, 34.6% had lymphopenia. Low B cell counts (74.8%) were the most common, followed by low numbers of T cells (28.4%) and NK cells (18.1%). CD4⁺ T cell deficiency was reported in 64.8% of the APDS patients. In addition, 88.3% of the patients showed reduced naive CD4⁺ T cells (CD4⁺CD45RA⁺). Although 14.5% of the patients had low CD8⁺ T cells, 30.9% showed increased numbers and 76.5% had raised numbers of activated CD8⁺ T cells (CD8⁺CD45RO⁺). Overall, APDS1 individuals had lower T

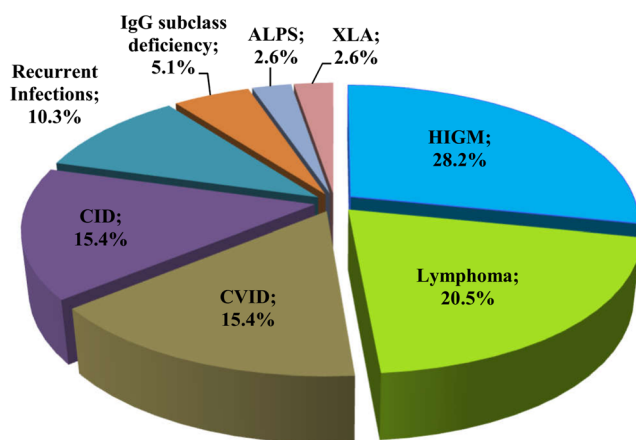


Fig. 1 Distribution of available primary clinical diagnosis of 39 APDS patients. Patients with APDS are often diagnosed with HIGM or lymphoma. HIGM hyperimmunoglobulin M, CVID common variable immunodeficiency, CID combined immune deficiency, ALPS autoimmune lymphoproliferative syndrome, XLA X-linked agammaglobulinemia

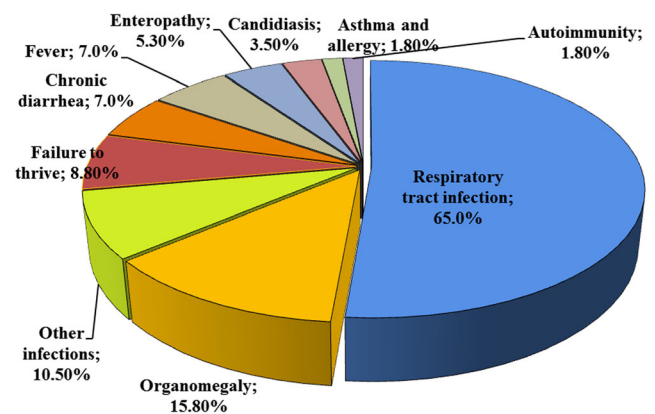


Fig. 2 Type of first clinical manifestations in APDS patients. The most common first presentations in APDS patients reported are respiratory tract infections and organomegaly

Table 2 Clinical manifestations of patients with APDS

Parameters	Total	APDS1	APDS2	<i>p</i> value
Pneumonia (%)	106 (43.6)	66 (36.9)	40 (62.5)	< 0.001*
Otitis (%)	70 (28.8)	53 (29.6)	17 (26.6)	0.644
Sinusitis (%)	63 (25.9)	53 (29.6)	10 (15.6)	0.028*
Meningitis (%)	6 (2.5)	6 (3.4)	0.0	0.345
Diarrhea (%)	39 (16)	27 (15.1)	12 (18.8)	0.493
Bronchiectasis (%)	69 (28.4)	61 (34.1)	8 (12.5)	0.001*
Abscess (%)	13 (5.3)	12 (6.7)	1 (1.6)	0.193
Septicemia (%)	13 (5.3)	10 (5.6)	3 (4.7)	1.0
Fungal infection (%)	21 (8.6)	17 (9.5)	4 (6.3)	0.427
Enteropathy (%)	65 (26.7)	51 (28.5)	14 (21.9)	0.305
Arthritis (%)	4 (1.6)	3 (1.7)	1 (1.6)	1.0
Autoimmunity (%)	69 (28.4)	56 (31.3)	13 (20.3)	0.095
Lymphadenopathy (%)	149 (61.3)	100 (55.9)	49 (76.6)	0.004*
Splenomegaly (%)	115 (47.3)	90 (50.3)	25 (39.1)	0.123
Hepatomegaly (%)	70 (28.8)	62 (34.6)	8 (12.5)	0.001*
Failure to thrive (%)	50 (20.6)	17 (9.5)	33 (51.6)	< 0.001*
Endocrinopathies (%)	13 (5.3)	11 (6.1)	2 (3.1)	0.523
Granulomatous lesions (%)	4 (1.6)	3 (1.7)	1 (1.6)	1.0
Malignancy (%)	31 (12.8)	19 (10.6)	12 (18.8)	0.094
Allergy and asthma (%)	15 (6.2)	14 (7.8)	1 (1.6)	0.125
Eye infection (%)	26 (10.7)	13 (7.3)	13 (20.3)	0.004*
Neurologic abnormality (%)	34 (14)	17 (9.5)	17 (26.6)	0.001*
ENT problem (%)	86 (35.7)	62 (34.8)	24 (38.1)	0.642
Hepatobiliary disorders (%)	17 (7)	13 (7.3)	4 (6.3)	1.0
Orthopedic abnormalities (%)	15 (6.2)	8 (4.5)	7 (10.9)	0.075
Dental problem (%)	10 (4.1)	7 (3.9)	3 (4.7)	0.726
BCGosis (%)	4 (1.6)	2 (1.1)	2 (3.1)	0.284

**p* value is statistically significant < 0.05

cell counts than APDS2 ($p = < 0.001$) and the CD4/CD8 index was inverted in both APDS1 (68.8%) and APDS2 (66%) patients. Evaluation of the B cell compartment revealed low class-switched memory B cells in 32 (53.3%) of 60 patients and expansion of transitional B cells in 52 (83.9%) of 62 patients. Adjusted to the age-matched normal ranges, low IgG, IgA serum levels, and raised IgM levels were observed in 102 (57.6%), 98 (57.3%), and 107 (60.5%) patients, respectively, and 78 patients (48.1%) showed a HIGM phenotype. This HIGM immunophenotype was more prevalent in the APDS2 group when compared to the APDS1 group (63% vs. 40.7%, $p < 0.001$). Overall, 15.4% showed normal IgG, IgA, and IgM levels; 4.3% had selective IgA deficiency; 15.4% hypogammaglobulinemia; and 16.6% IgG subclass deficiency.

Molecular Findings of APDS Patients

Among 243 patients reported with APDS in 191 families, 179 patients had mutations in the *PIK3CD* gene

and 64 patients in the *PIK3RI* gene. We did not have access to the mutations of four patients, as in one APDS1 case, the mutation was not reported and in three APDS2 cases the family relationships were not declared [8, 10]. Altogether, 23 different DNA mutations (11 in *PIK3CD* and 12 in *PIK3RI* genes) were reported. Despite the different mutations at the coding DNA level, these 23 different mutations resulted in 11 (*PIK3CD*) and 2 (*PIK3RI*) types of protein changes (Table 4). This data suggests that the APDS1 causing mutation c.3061 G>A (p. E1021K) with a frequency of 85% and the APDS2 causing mutation c.1425+1 G> (A, C, T) (p.434–475del) with a frequency of 79% were hotspot mutations. Recurrent de novo mutations were frequently observed in the APDS1 [1, 2, 11–19] and APDS2 [4, 8, 20–25], and this does not seem to be due to a founder effect [1]. All mutations in *PIK3CD* gene were missense, while nearly all mutations in *PIK3RI* gene were splice site mutation except one missense mutation. Of the 11 splice site mutations, only one affected the splice acceptor site and 10 affected the splice donor site (Fig. 4).

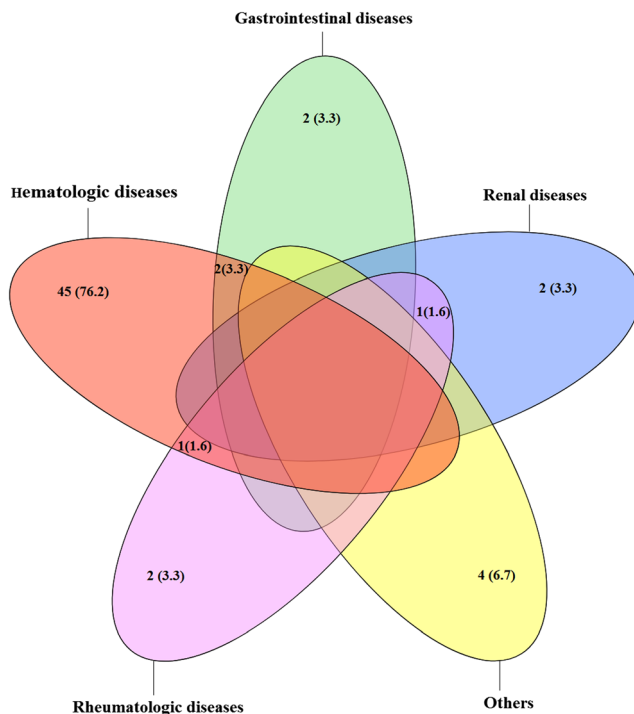


Fig. 3 Venn diagram showing multiorgan autoimmune manifestations in APDS patients. Autoimmune manifestations were reported in 68 patients (although in 9 patients no details were available). Hematologic manifestations (immune thrombocytopenic purpura, autoimmune hemolytic anemia, neutropenia, Evans syndrome), gastrointestinal manifestations (autoimmune hepatitis and inflammatory bowel disease), renal manifestations (glomerulonephritis and lupus-like nephritis), rheumatologic diseases (Sjögren's syndrome, juvenile idiopathic arthritis and SLE-like disease), and other manifestations (diabetes mellitus type 1, autoimmune thyroiditis, and psoriasis) have been observed in APDS patients. The combination gastrointestinal symptoms with autoimmune hematologic manifestations were the most common

The Therapeutic Approach in APDS Patients

Following the diagnosis of PID or as a symptomatic treatment approach, intravenous Ig (IVIg) replacement therapy was initiated in 151 (62.9%) patients. High dose IVIg (hdIVIg) was used to treat ITP and AIHA in 38 (84.4%) patients. Anti-inflammatory drugs such as corticosteroids were often first-line therapy for autoimmunity and inflammation. Immunosuppressive drugs such as mycophenolate mofetil and rituximab were also frequently prescribed. The emerging new targeted ADPS treatment option such as rapamycin (sirolimus) or leniolisib, which is a PI3K δ inhibitor, was used in 29 (11.9%) patients. Furthermore, allogeneic hematopoietic stem cell transplantation (HSCT) with HLA identical donors was performed in 31 (12.8%) patients at the median (IQR) age of 9.5 (8.0–14.7) years. Among HSCT complications, acute or chronic GVHD occurred in about 45% of the transplants. Other organ transplantations (kidney and liver) were reported in four (1.6%) cases. Moreover, tonsillectomy and/or adenoidectomy were performed in 21 (8.6%) patients, and 10 (4.1%) patients had undergone splenectomy.

Discussion

The present study was designed to systematically review the clinical, immunological, and molecular characteristics of APDS patients. Most of the patients were initially diagnosed as HIGM syndrome. Impaired cellular immunity was observed more frequently in APDS1 patients, whereas the humoral arm of the immune system including B cell and subsequent antibody production was mostly affected in APDS2 individuals. To date, more than 240 APDS patients have been reported in the literature with a broad spectrum of clinical manifestations including recurrent respiratory infections, lymphoproliferation, autoimmunity, enteropathy, and increased risk of malignancies (particularly lymphoma); however, chronic infections, especially of the respiratory tract, in the first year of life are the most common clinical manifestations.

The predominant immunologic phenotype suggested a HIGM syndrome in 48%, and not surprisingly, 28% of the patients were initially diagnosed with a HIGM syndrome as many of these patients also had progressive B- and T cell lymphopenia or CSR defects following disturbed germinal center architecture [8]. This is in line with previous cohort studies reporting increased IgM levels in APDS patients [7, 8, 11, 20]. We, therefore, suggest to add *PIK3CD* and *PIK3R1* mutations to the differential diagnosis in patients presenting respiratory infections, lymphadenopathy, and an immunological phenotype compatible with a HIGM syndrome, along with the list of genes known to be associated with CSR defects and somatic hypermutation (*AICDA*, *CD40*, *CD40L*, and *NEMO*).

As noted in the result section, the bronchiectasis prevalence was higher in patients with APDS1 in spite of lower prevalence of pneumonia in this group. On the other hand, about half of all APDS patients who developed bronchiectasis had no history of pneumonia.

Since most of the bronchiectasis in immunodeficiency is expected to be post-infectious, this may be due to issues with pneumonia diagnosis and/or reporting. However, it can be proposed that other etiologies may have predisposed these patients to the development of airway damages such as bronchial obstruction secondary to respiratory tract lymphoid proliferation and inflammatory processes involved in autoimmunity, both of which were more frequent in APDS1 patients. In addition, p110 δ overexpression may itself contribute to airway remodeling in APDS1 patients as previous studies have shown that inhibition of p110 δ isoform via IC87114 reduces the production of contractile proteins α -SMA and calponin and release of proinflammatory cytokine IL-6 [26, 27]. Altogether, we suggest assessment of patients with chest computed tomography (CT) scan during early stages of disease as a considerable number of patients develop bronchiectasis without preceding pneumonia.

As with previous studies, we found that growth disorders were significantly more frequent in APDS2 comparing to

Table 3 Immunologic profile of patients with APDS

Parameters	Total	APDS1	APDS2	<i>p</i> value
WBC $\times 10^3$ (cell/ μ L), median (IQR) (<i>n</i> = 32)	5.50 (4.30–7.95)	5.45 (4.3–7.75)	7.4 (2.8–9.75)	0.393
Absolute lymphocytes counts $\times 10^3$ (cells/ μ L), median (IQR) (<i>n</i> = 85)	1.34 (1.01–1.94)	1.29 (1.0–1.91)	1.5 (1.2–2.1)	0.259
Absolute neutrophil counts $\times 10^3$ (cells/ μ L), median (IQR) (<i>n</i> = 7)	4.48 (2.68–5.0)	4.69 (2.99–5.37)	1.15	0.134
IgG, mg/dL, median (IQR) (<i>n</i> = 146)	504.5 (113.5–940)	720 (387.5–1094.5)	90 (25.5–419.5)	< 0.001*
IgA (mg/dL), median (IQR) (<i>n</i> = 145)	23 (5.5–86.5)	51 (15–107)	5.5 (2.2–9.0)	< 0.001*
IgM (mg/dL), median (IQR) (<i>n</i> = 149)	250 (153–434.5)	265 (178–474.7)	199 (109–367)	0.012*
CD3 ⁺ T cells (cell/ μ L), median (IQR) (<i>n</i> = 131)	1108 (721–1754)	926.5 (657.7–1227)	1793 (1178–2363)	< 0.001*
CD4 ⁺ T cells (cell/ μ L), median (IQR) (<i>n</i> = 131)	438 (310–710)	379.9 (250.4–519.3)	696 (400–833)	< 0.001*
CD4CD45RO (cell/ μ L), median (IQR) (<i>n</i> = 17)	283.3 (155.5–333.4)	283.3 (155.5–317.3)	431.8 (148.1–602.6)	0.365
CD4CD45RA (cell/ μ L), median (IQR) (<i>n</i> = 40)	73.7 (26.3–140.9)	72.1 (25.7–130.2)	88 (22.6–169.7)	0.452
CD8 ⁺ T cells (cell/ μ L), median (IQR) (<i>n</i> = 125)	571.3 (340.5–951.5)	460.5 (315.7–676)	932.5 (476–1380)	< 0.001*
CD8CD45RO (cell/ μ L), median (min–max) (<i>n</i> = 3)	155.4 (35.2–760.2)	95.3 (35.2–155.4)	760.2	0.221
CD8CD45RA (cell/ μ L), median (IQR) (<i>n</i> = 18)	48.7 (33.4–135.8)	48.7 (36.6–117.4)	48.4 (23.6–177.6)	0.925
Regulatory T cells (cell/ μ L), median (IQR) (<i>n</i> = 13)	28.9 (18.9–38.2)	28.9 (18.9–38.2)	NA	–
NK cell, (cell/ μ L), median (IQR) (19.4%, <i>n</i> = 57)	210 (117–360)	186 (101.0–380.5)	235 (163.7–350)	0.258
CD19 ⁺ B cells (cell/ μ L), median (IQR) (<i>n</i> = 128)	95 (40.6–196.9)	95 (49.1–210.1)	97.5 (36.2–180)	0.264
Transitional B cell, (CD19 ⁺ CD27 ^{int} CD38 ⁺⁺ IgM ⁺⁺), (cell/ μ L), median (IQR) (<i>n</i> = 31)	46 (6.0–92.8)	60.4 (20.5–107.7)	26.2 (3.6–71.1)	0.296
Naïve B cell, (CD19 ⁺ CD27 [−] IgM ⁺ IgD ⁺), (cell/ μ L), median (min–max) (<i>n</i> = 20)	78.4 (18.9–127.5)	72 (16.4–167.7)	106.2 (23.7–109.5)	0.791
Marginal zone B cell, (CD19 ⁺ CD27 ⁺ IgM ⁺⁺ IgD ⁺), (cell/ μ L), median (IQR) (<i>n</i> = 9)	6.6 (2.4–18.5)	NA	6.6 (2.4–18.5)	–
Switched memory B cell, (CD19 ⁺ CD27 ⁺ IgM [−] IgD [−]), (cell/ μ L), median (IQR) (<i>n</i> = 46)	7.03 (1.12–25.28)	7.1 (3.3–27.2)	5.2 (0.79–25.1)	0.634
Memory B cells, (cell/ μ L), median (IQR) (<i>n</i> = 38)	11.7 (3.9–25.4)	14 (4–28.1)	7.7 (2.6–23.5)	0.258
Defective anti-peptide Ab response (%) (<i>n</i> = 42)	14 (33.3)	10 (27.8)	4 (66.7)	0.155
Defective anti-polysaccharide Ab response (%) (<i>n</i> = 58)	52 (89.7)	47 (88.7)	5 (100)	1.0

The median is shown (with 25th and 75th percentiles)

Ig immunoglobulin, WBC white blood cell, NK cell natural killer cell, NA not available

**p* value is statistically significant < 0.05

APDS1. Moreover, three APDS2 patients also suffered from SHORT syndrome [28, 29] while no association between SHORT syndrome and APDS1 was reported. As some of the APDS2 patients presented features such as poor growth, learning disability, microcephaly, and glucose metabolism impairment, under-diagnosis of SHORT syndrome in this group is possible. The role of *PIK3RI* in growth disorders has been investigated previously [30]. It has been proposed that high amounts of monomeric P85 α compete with the p85-p110 dimer for the binding to the tyrosine-phosphorylated IRS-1, leading to ineffective activation of the insulin and insulin-like growth factor (IGF)-1 [31]. In addition, the role of other catalytic PI3K subunits such as p110 α and negative feedback mechanisms due to chronic overactivation of the PI3K pathway are also feasible mechanisms that would explain the growth restriction in APDS patients [28]. However, growth hormone therapy is not suggested, as growth hormone receptor activation further stimulates the PI-3 kinase pathway [32].

Malignancy is one of the major complications of APDS. Thirty-one malignancies were reported in 243 APDS patients, and lymphoma (in particular diffuse large B cell lymphoma (DLBCL)) was the most common type of malignancy (89%). This is in line with the findings of the previous studies [7–9, 33]. The PI3K/Akt/mTOR pathway has a pivotal role in controlling proliferation and survival of tumor cells. In particular, class I PI3K plays a crucial role in oncogenesis [34]. In addition, (chronic) viral infections may contribute to this preexisting tumor risk. Our result showed that about half of the reported APDS patients (48.1%) had at least one episode of viral infection and that the risk to develop lymphomas was significantly higher in patients with a previous history of viral infections especially EBV. EBV has a particular affinity to B cells and that these act as reservoir for the virus [35, 36]. Moreover, underlying immune dysregulation prevents effective viral elimination and creates a hostile inflammatory environment further stimulating cell survival and proliferation

Table 4 Mutation spectrum of APDS patients

Gene	Mutation	Protein	Patient(s)*	Percentage
<i>PIK3CD</i>	c.241 G>A	p.E81K	2	1.5
	c.371 G>A	p.G124D	3	2.2
	c.1002 C>A	p.N334K	1	0.7
	c.1213 C>T	p.R405C	1	0.7
	c.1246 T>C	p.C416R	1	0.7
	c.1570 T>A	p.Y524N	2	1.5
	c.1573 G>A	p.E525K	5	3.7
	c.1574 A>C	p.E525A	3	2.2
	c.27845 C>T	p.R929C	1	0.7
	c.3061 G>A	p.E1021K	115	84.6
	c.3074 A>G	p.E1025G	2	1.5
Total	11	11	136	100.0
<i>PIK3RI</i>	c.1299+1 G>A	p.434–475del	1	1.9
	c.1300-1 G>C	p.434–475del	1	1.9
	c.1418_1425+1del	p.434–475del	1	1.9
	c.1425+1 G>A	p.434–475del	27	50.9
	c.1425+1 G>C	p.434–475del	8	15.1
	c.1425+1 G>T	p.434–475del	7	13.2
	c.1425+2 A>T	p.434–475del	1	1.9
	c.1425+2 T>A	p.434–475del	3	5.7
	c.1425+2 T>G	p.434–475del	1	1.9
	c.1425-1 G>C	p.434–475del	1	1.9
	c.1425+2,3 TGdel	p.434–475del	1	1.9
c.1692 C>G	p.N564K	1	1.9	
Total	12	2	53	100.0

*The mutations present in several patients from one family were counted as one mutation

[37–39]. This dysregulation in APDS1 patients involves exhaustion, senescence, and diminished cytotoxicity of CD8⁺ T and NK cells induced by PIK3CD mutation which may increase herpesviruses susceptibility and tumor surveillance [9].

Unfortunately, the PI3K/AKT/mTOR activation is an unfavorable prognostic factor for DLBCL [40] and in our study, 66.6% of patients who died of lymphoma received a diagnosis of DLBCL. Therefore, periodic EBV screening and

considering the risk of lymphoma in those with a history of chronic EBV infection may be beneficial for APDS patients. Nevertheless, further cohort studies are needed to investigate to what extent EBV infections predict risk of developing malignancy in the future.

In APDS, gain of function (GOF) mutations in PI3K δ either in the leukocyte-restricted p110 δ catalytic (*PIK3CD*) subunit or in the ubiquitously expressed p85 α regulatory (*PIK3RI*) subunit leads to APDS1 and APDS2, respectively. In spite of heterozygous loss-of-function (LOF) mutations in *PIK3RI*, due to the net outcome of increased PI3K δ activity, these are also considered GOF mutations [41]. Homozygous loss-of-function mutations either in *PIK3RI* [42, 43] or in *PIK3CD* [44] result in different PID entities with PI3K δ deficiency and autosomal recessive inheritance. Since the early publications, 11 activating missense mutations in the *PIK3CD* gene, one splice site, and one missense mutation in *PIK3RI* gene have been reported (Table 4). These mutations augment PI3K δ activity through enhancing membrane association and kinase activity (E1021K [1, 45], E1025G, and R929C [19, 46, 47]), increasing kinase activity through conformational changing (E81K and G124D [48]), interrupting inhibitory interaction between p110 δ helical domain and the p85 α nSH2 domain (E525K, E525A, and Y524N [2, 18, 49]) and between p85 α iSH2 domain and p110 δ C2 domain (N334K, R405C, and C416R [2, 50]). Accordingly, two mutations in iSH2 domain of p85 α (434–475 deletion and N564K) interrupt inhibitory function of this protein [47, 50] and also diminish proteins stability [12]. PIK3CD and PIK3RI GOF variants display genetic pleiotropy and their mutations also have oncogenic potential [51, 52]. Mutations in p110 δ are found in analogous locations to oncogenic mutations in p110 α [48]. P85 α acts as a tumor suppressor; hence, mutations in this protein may drive cancer development through p110 α hyperactivation [53, 54]. Several mutations in p85 α have been reported in the context of endometrial cancer [55], glioma [56], and colon cancer [57]. Interestingly, the p.N564K mutation (that reported in APDS2) is an oncotic mutation in endometrial [58] and breast [59] cancers, while p.434–475del has not been reported in cancerous samples [60]. Considering the different impacts of

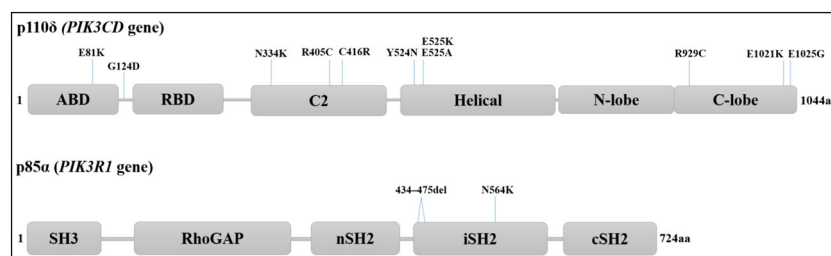


Fig. 4 Schematic diagram of the p110 δ and p85 α protein domains and positions of mutations. Adaptor-binding domain (ABD); Ras-binding domain (RBD); N-terminal lobe (N-lobe); C-terminal lobe (C-lobe);

SRC homology domain (SH); Rho GTPase-activating protein (RhoGAP); N-terminal SH2 (cSH2); interSH2 (iSH2); C-terminal SH2 (cSH2)

p85 α mutations on p110 δ and p110 α activity [45], it is maybe not surprising that these oncogenic mutations are restricted in lymphoma.

The therapeutic approach in APDS patients includes prophylactic antibiotics, immunoglobulin replacement therapy, use of immunosuppressive agents, and HSCT. Different immunosuppressive agents have been used to control autoimmune and inflammatory complications. About one-third of the reported APDS patients had autoimmune complications and received at least one course of immunosuppressive agents including steroids, rapamycin, rituximab, mycophenolate mofetil, tacrolimus, azathioprine, and cyclosporine. Prednisolone in combination with mesalazine improved the inflammatory bowel disease [61] in one patient, and rituximab reduced non-neoplastic lymphoproliferation in five APDS cases [7]. Among the immunosuppressive agents, rapamycin was shown to ameliorate the severity of benign lymphoproliferative manifestations and improve immunologic markers in APDS [25, 62, 63] while APDS-related cytopenia and GI inflammation responded less well [63]. Rapamycin has also shown to restore the NK cell function, which is likely relevant in the context of the known susceptibility to viral infections [64]. However, long-term side effects of rapamycin need to be monitored as one patient developed a lymphoma under rapamycin therapy [63]. By getting more familiar with the underlying mechanism of APDS, several targeted therapies have been proposed; however, because of limited experiences, it remains to be seen to what extent these therapies will lead to a significant clinical benefit. Selective PI3K δ inhibitors have been suggested to provide greater efficacy and fewer side effects. Rao et al. [65] investigated the therapeutic effect of Leniolisib (CDZ173) in APDS individuals and observed normalization of circulating transitional and naïve B cells, reduction in senescent T cells, decreases in elevated serum IgM levels, and cytokine/chemokine modulation. Furthermore, after 3 months of therapy, lymph node and spleen sizes reduced and an increase of well-being was reported in all patients [64]. The patients received treatment for over 9 months, and during this period, no significant side effects have been detected [65, 66]. Another PI3K δ inhibitor Idelalisib (GS-1101) has shown to reduce hyperactivity of the mutant PI3K δ , but the in vivo function remains to be surveyed in future studies [45]. Nemoralisib as a PI3K δ inhibitor has been shown to improve the survival of mice with early *Streptococcus pneumoniae* infection and reduce IL-10 levels in the lung [67]. PI3K δ hyperactivation promotes the development of CD19⁺B220⁻ cells that are functionally considered equivalent to the expanded transitional B cells in APDS patients. Both cell types produce IL-10 leading to an increased susceptibility to *S. pneumoniae* infections. Therefore, it is postulated that nemoralisib may also prevent *S. pneumoniae* infection in APDS patients. Inhaled nemoralisib is currently being investigated in APDS patients and has been proposed to benefit patients primarily affected

by airway infection and bronchiectasis. However, this ongoing clinical trial has not reported any results yet [67]. Recently, it has been shown that APDS mouse model exhibited aberrant autoantibody production against commensal microbiome which considerably controlled with antibiotics [68]. This may imply modification of gut microbiota as a treatment option for autoimmune manifestations in APDS patients.

HSCT in APDS patients has been specifically evaluated in two unrelated studies [69, 70]. Age at transplant ranged from 4 to 18 years. HLA-matched donors were used in 45.5% (71) and 80% (70) of individuals. Most cases, especially younger patients, improved their clinical symptoms in particular infection susceptibility, lymphoproliferation, hypogammaglobinemia, and enteropathy. Most of the patients (71.4% (70) and 100% (71)) were weaned of IVIG by day 100. However, adverse complications (90% (70) and 90.9% (71)) and engraftment failure (0% (70) and 36.4% (71)) were frequent, and graft versus host disease occurred in five and nine patients, respectively. Furthermore, HSCT carried a mortality risk of 10–20% and two patients in each study died from sepsis, multiorgan failure, CMV/adenovirus pneumonitis, and idiopathic pneumonitis [69, 70]. This indicates that HSCT should likely be restricted to those APDS patients with severe and complicated clinical manifestations with no or insufficient response to the currently available conventional therapies.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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