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Clinical practice guideline for activated phosphatidyl inositol 3-kinase-delta syndrome in Japan

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ABSTRACT

Activated phosphatidyl inositol 3-kinase-delta syndrome (APDS) due to gain-of-function variant in the class IA PI3K catalytic subunit p110δ (responsible gene: PIK3CD) was described in 2013. The disease is characterized by recurrent airway infections and bronchiectasis. It is associated with hyper-IgM syndrome due to the defect of immunoglobulin class switch recombination and decreased CD27-positive memory B cells. Patients also suffered from immune dysregulations, such as lymphadenopathy, autoimmune cytopenia or enteropathy. T-cell dysfunction due to increased senescence is associated with a decrease in CD4-positive T lymphocytes and CD45RA-positive naive T lymphocytes, along with increased susceptibility to Epstein-Barr virus/cytomegalovirus infections. In 2014, loss-of-function (LOF) mutation of p85α (responsible gene: PIK3R1), a regulatory subunit of p110δ, was identified as a causative gene, followed in 2016 by the identification of the LOF mutation of PTEN, which dephosphorylates PIP3, leading to the differentiation of APDS1 (PIK3CD-GOF), APDS2 (PIK3R1-LOF) and APDS-L (PTEN-LOF). Since the pathophysiology of patients with APDS varies with a wide range of severity, it is crucial that patients receive appropriate treatment and management. Our research group created a disease outline and a diagnostic flow chart and summarized clinical information such as the severity classification of APDS and treatment options.

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APDS; hyper-IgM syndrome; immune dysregulations; diagnostic flow chart

1. Introduction

Inborn errors of immunity (IEI) are a group of disorders that cause increased susceptibility to infections and immune dysregulation. To date, variants of almost 500 responsible genes have been shown to cause various IEI [1]. Activated phosphatidyl inositol 3-kinase (PI3K)-delta syndrome (APDS) is an IEI for which the causative gene was discovered in 2013. It is reported as a disease caused by gain-of-function variants in the Class IA PI3K catalytic subunit p110δ (responsible gene: PIK3CD) [2,3]. The disease is characterized by recurrent airway infections and bronchiectasis beginning in childhood, and many patients present with lymphadenopathy, enteropathy and autoimmune diseases. Immunologically, aberrant antibody production (i.e., high IgM, low IgG, IgG2, low IgA) leading to hyper-IgM syndrome (HIGM) is observed, along with increased susceptibility to opportunistic infections, such as Epstein–Barr virus (EBV) or cytomegalovirus (CMV) infections. Flow cytometry analysis of peripheral blood lymphocytes shows T-cell dysfunction decrease in CD4-positive T lymphocytes and CD45RA-positive naive T lymphocytes, decrease in CD27-positive memory B cells and increase in CD24-high CD38-high CD10-positive transitional B cells [2,3].

Furthermore, in 2014, a loss-of-function variant of p85α (responsible gene: *PIK3R1*), a regulatory subunit of p110δ, was identified in patients with symptoms similar to APDS [4,5]. Disorders caused by gain-of-function variants in the *PIK3CD* gene are now categorized as APDS type 1 (APDS1), and those caused by loss-of-function variants in *PIK3R1* are categorized as APDS type 2 (APDS2). In 2016, APDS-like condition caused by loss-of-function variants in *PTEN* was identified. Since PTEN catalyzes the dephosphorylation reaction of PIP3 and suppresses the AKT/mTOR/S6 pathway, loss-of-function mutations in *PTEN* cause overexpression of PIP3, resulting in a clinical condition similar to

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APDS [6]. *PTEN* mutation was found in several phenotypically defined syndromes (Cowden syndrome 1, Lhermitte-Duclos disease, Macrocephaly/autism syndrome, PTEN Hamartoma tumor syndrome, Bannayan-Riley-Ruvalcaba Syndrome, etc.) described two patients with immunodeficiency and found the PTEN loss of function mutations [6]. They had mental retardation with macrocephaly as seen in other *PTEN* mutated patients diagnosed as Macrocephaly/autism syndrome but they lacked the phenotype of hamartoma, the hallmark of Cowden syndrome. On the other hand, immunological phenotype was similar to recently described APDS.

Variants in either subunit cause APDS, with over 250 reported patients and many more not reported in the literature. APDS1 and APDS2 consist of approximately 75% and 25%, respectively [2–6]. These variants lead to immunodeficiency with recurrent infections by multiple pathogens (bacterial, viral and other) affecting multiple organ systems.

In APDS, overexpression of PIP3 caused by constant activation of class IA PI3K induces overactivation of the PI3K signaling pathway, leading to hyperphosphorylation of the downstream AKT/mTOR/S6 [2–5]. AKT is an important molecule that controls cell proliferation, differentiation, growth and metabolism, and hyperphosphorylation causes abnormal activation of lymphocytes and enlargement of lymphatic tissue [7]. As *PTEN* suppresses PI3K, when this function is impaired by a *PTEN* gene variant, PI3K becomes dominant, causing a pathological condition similar to APDS [6]. Based on the current knowledge and experiences in Japan, we (the expert committee of IEI supported by a grant from the Ministry of Health, Labor and Welfare) made the Clinical Practice Guideline for APDS in Japan.

2. Methods

To create an APDS clinical practice guideline based on Minds, we utilized a literature search system to conduct a literature review of past reports on APDS, summarized clinical and laboratory findings and formulated a clinical practice guideline. We conducted a search of articles published on PubMed before 16 December 2020 and selected 15 articles of significance as references. The search terms and results are as follows:

1. 'Activated PI3K-delta syndrome'–61 results
2. 'Activated PI3K-delta syndrome 'AND 'PIK3CD'–37 results
3. 'Activated PI3K-delta syndrome 'AND 'PIK3R1'–17 results
4. 'Activated PI3K-delta syndrome 'AND 'PTEN'–2 results
5. 'Activated PI3K-delta syndrome' AND 'Hyper-IgM'–3 results
6. 'Activated PI3K-delta syndrome' AND 'Treatment'–19 results
7. 'Activated PI3K-delta syndrome' AND 'Stem cell transplantation'–11 results

3. Clinical presentations

1. Recurrent lower respiratory tract infections, sinusitis, otitis media and bronchiectasis starting in early childhood
2. Systemic lymphadenopathy, lymphoid hyperplasia
3. Increased susceptibility to EBV/CMV or other opportunistic infections (persistent and/or severe infection)

4. Physical findings

The patient presents with systemic lymphadenopathy, hepatosplenomegaly and intestinal follicular hyperplasia.

5. Laboratory findings

1. Serum immunoglobulin levels show low IgG (especially IgG2), low IgA and normal to high IgM.
2. Normal to decreased peripheral B cells, decreased CD27-positive memory B cells, increased CD24-high CD38-high IgM-positive transitional B-cell fraction
3. Decreased CD4-positive T cells, decreased CD45RA-positive naive T cells, increased CD8-positive effector memory T cells, increased follicular T cells (TFH) and increased CD57-positive CD8 T cells
4. *PIK3CD* gene gain-of-function variants (hot spots in N334K, C416R, E1021K)
5. *PIK3RI* gene loss-of-function variants (i.e., splice site mutations that cause exon 11 skipping on p85α)
6. *PTEN* loss-of-function variants
7. Increased phosphorylation of AKT, mTOR and ribosomal protein S6 (RPS6) proteins (Figure 1).

6. Differential diagnosis

It has been reported that a considerable number of cases of APDS are included in cases clinically diagnosed as HIGM or common variable immunodeficiency (CVID). The possibility of APDS should be considered in patients with HIGM or CVID where the causative gene has not been identified.

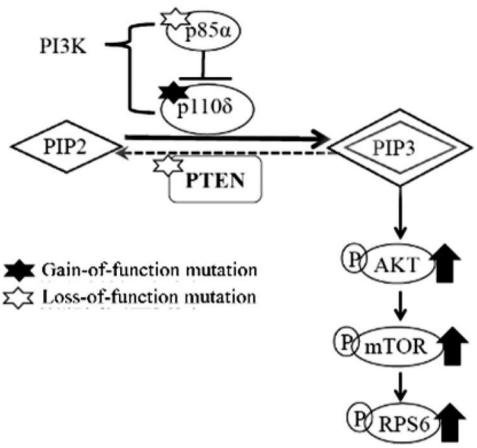

Figure 1. Hyperphosphorylation of AKT/mTOR/S6 pathway in APDS.

7. Severity classification

Cases with increased susceptibility to infections due to antibody deficiency are considered 'severe', and regular immunoglobulin supplementation and administration of prophylactic antibacterial agents are essential.

Cases that require treatment for immune dysregulation, lymphoid organ hyperplasia or regular monitoring of complications are also considered 'severe'.

Mutation-positive family members with no or mild symptoms can be considered 'mild'.

8. Complications

Hepatosplenomegaly, lymphoid hyperplasia and bronchiectasis are common complications seen in all types of APDS [8,9]. Failure to thrive and mild mental retardation have been reported in approximately 50% of patients with APDS2. Additionally, malignant tumors (especially B-cell lymphoma), autoimmune diseases (i.e., cytopenia), bronchiectasis and chronic diarrhea are observed [9]. Mild mental retardation and macrocephaly are observed in patients with APDS-L [6].

9. Diagnosis

In patients with recurrent sinusitis, lower airway infection and hepatosplenomegaly or lymphoid hyperplasia, APDS can be determined by immunological evaluations, such as low levels of IgG, IgG2, IgA and/or high IgM, and findings from peripheral blood flow cytometry, such as decreased CD4-positive T cells, decreased CD45RA-positive naive T cells, increased TFH, decreased memory B cells and increased transitional B cells. Macrocephaly and mental retardation should also be considered complications.

Definitive diagnosis is made by genetic testing and confirming increased phosphorylation of AKT and S6 proteins in activated T lymphocytes or B lymphocytes of the patient.

Diagnosis flow chart is shown in Figure 2.

10. Treatment

For immunocompromised patients with antibody deficiency, regular immunoglobulin supplementation and administration of prophylactic antibacterial drugs such as trimethoprim/sulfamethoxazole and low-dose macrolides are strongly recommended. Antiviral prophylaxis by acyclovir or ganciclovir and regular monitoring of EBV/CMV infections should also be implemented. Allogeneic hematopoietic cell transplantation (HCT) can be considered in cases with T-cell dysfunction or dysregulation, massive lymphoid organ hyperplasia or malignant lymphoma. In some cases, immunosuppressive therapy (i.e., rituximab, sirolimus) may be necessary for autoimmune diseases [8–13].

In recent years, there have been reports of cases in which mTOR inhibitors and selective p110δ inhibitors were effective against lymphoid hyperplasia or immune dysregulation in patients with APDS. Several studies have reported that rituximab is effective for the treatment of lymphoid hyperplasia, such as lymphadenopathy and hepatosplenomegaly, often seen in patients with APDS. However, rituximab should be cautiously considered, because it can cause persistent, often permanent, B-cell depletion. In recent years, mTOR inhibitors (sirolimus) [14] and selective p110δ inhibitors (i.e., leniolisib) [15] have also been reported to be effective. mTOR inhibitors have been shown to reduce hepatosplenomegaly and lymphadenopathy, increase the naive T-cell fraction and restore T-cell proliferation and IL-2 secretion [14]. Maccari et al. [14] reported that of 25 patients, eight achieved complete remission and 11 achieved partial remission. However, relapse after completion of treatment and side effects of long-term use have also been reported.

On the other hand, selective p110δ inhibitors are attracting attention as treatments that can reduce side effects and achieve higher efficacy. Rao et al. [15] reported that in six patients with APDS, after 12 weeks of treatment with leniolisib (oral medication), reduced lymphadenopathy (mean 40%) and splenomegaly (mean 39%) were observed in all patients. Furthermore, normalization of transitional B cells and serum IgM level was observed. The results from further research on this drug are anticipated.

HCT has also been performed in some cases to replace abnormal lymphocytes that cause persistent activation of PI3Kδ [10,11,16]. However, considerable

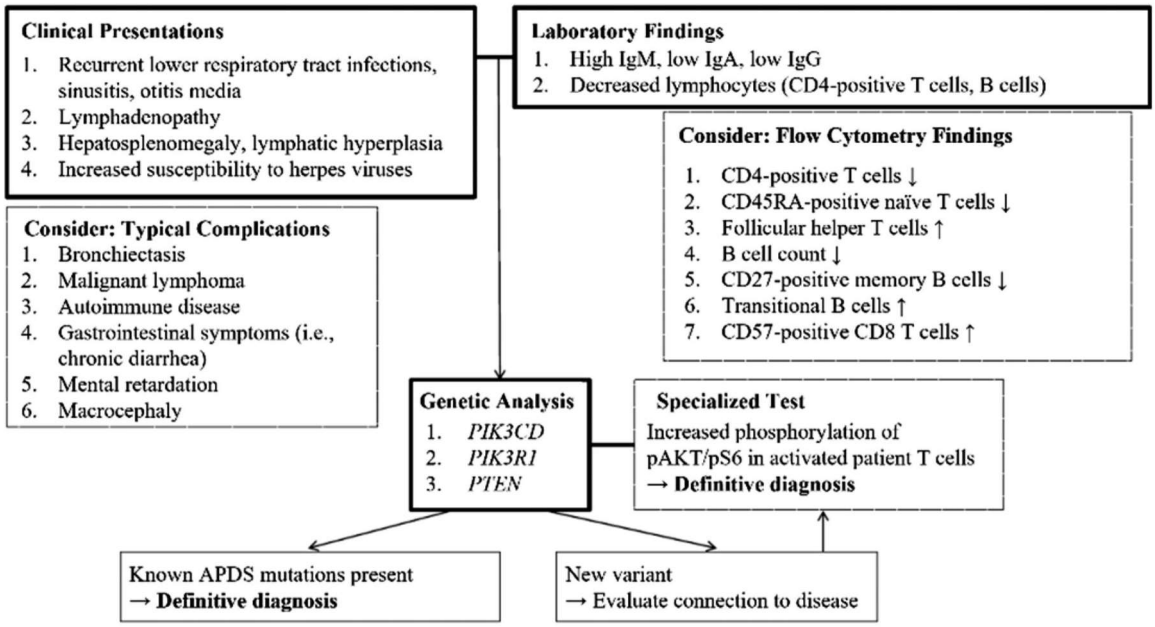

Figure 2. Diagnosis flow chart for APDS.

difficulty in management after HCT has been reported [11]. Further prospective studies to improve the prognosis of APDS patients are necessary.

11. Patient monitoring

1. Immunological evaluations: White blood cell count, lymphocyte count, lymphocyte subset analysis, serum IgG/IgG2/IgA/IgM, T-cell receptor excision circles (TRECs) and KRECs (Igκ-deleting recombination excision circles).
2. Monitoring of EBV/CMV infections: EBV-related antibody titer, CMV antigenemia test, blood EBV/CMV viral load assay.
3. Pulmonary function tests: Bronchiectasis due to repeated lower respiratory tract infections should be carefully monitored. Chest X-rays and chest CT scans should be evaluated as necessary.
4. Evaluation of lymphoid hyperplasia: Examine for tonsils and superficial and deep lymph nodes and hepatosplenomegaly, with assessments of imaging tests (i.e., CT/MRI, FDG-PET) as necessary.
5. Surveillance of malignant tumors: Carefully monitor for development of lymphoma.
6. Evaluations of other complications: Examine for enteropathy including the gastrointestinal fiber scope. Type 1 diabetes mellitus can be associated with APDS2 [17].

12. Considerations in clinical practice

1. While APDS is an autosomal dominant disorder, it can present with various clinical symptoms and laboratory findings even within the same family.
2. Patients with APDS2 have a high probability of developing malignant tumors (especially B-cell lymphoma) as a complication. Appropriate patient management and assessment by imaging tests is needed.

13. Prognosis and challenges in adulthood

The incidence of malignant tumors in APDS has been reported to be 13% for APDS1 and 28% for APDS2, with a particularly high incidence of B-cell lymphoma. In addition, 16% of patients with APDS die from lymphoma-related complications. Appropriate observation and treatment are directly linked to an improved prognosis [13]. Okano et al. [11] reported that in a study of 23 patients with APDS1, nine of whom received HCT, the OS at 30 years was 86.1%, and the event-free survival was 39.6%. Complications such as infections or lymphatic tissue enlargement were observed frequently in childhood and adolescence. In particular, a major challenge is the limited treatment options that are effective in treating lymphatic tissue enlargement. Elkeim et al. [9] reported that in 36 patients with APDS2, the median survival was 18 years (range 3–56 years), and of the five deaths, four were caused by malignant lymphoma.

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Author contributions

KM and KI conceived and designed the study. KM, KM-S and YS wrote the manuscript. AE, HK, TM and SN provided critical discussion, supervised the study and edited the manuscript. All authors reviewed the paper. All authors contributed to the article and approved the submitted version.

Disclosure statement

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References

[1] Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the international union of immunological societies expert committee. J Clin Immunol. 2022;42(7):1473–1507.
[2] Angulo I, Vadas O, Garçon F, et al. Phosphoinositide 3-kinase δ gene mutation predisposes to respiratory infection and airway damage. Science. 2013;342(6160):866–871.
[3] Lucas CL, Kuehn HS, Zhao F, et al. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110δ result in T cell senescence and human immunodeficiency. Nat Immunol. 2014;15(1):88–97.
[4] Deau MC, Heurtier L, Frange P, et al. A human immunodeficiency caused by mutations in the PIK3R1 gene. J Clin Invest. 2014;124(9):3923–3928.
[5] Lucas CL, Zhang Y, Venida A, et al. Heterozygous splice mutation in PIK3R1 causes human immunodeficiency with lymphoproliferation due to dominant activation of PI3K. J Exp Med. 2014;211(13):2537–2547.
[6] Tsujita Y, Mitsui-Sekinaka K, Imai K, et al. Phosphatase and tensin homolog (PTEN) mutation can cause activated phosphatidylinositol 3-kinase δ syndrome-like immunodeficiency. J Allergy Clin Immunol. 2016;138(6):1672.e10–1680.e10.
[7] Okkenhaug K, Vanhaesebroeck B. PI3K in lymphocyte development, differentiation and activation. Nat Rev Immunol. 2003;3(4):317–330.
[8] Coulter TI, Chandra A, Bacon CM, et al. Clinical spectrum and features of activated phosphoinositide 3-kinase d syndrome: a large patient cohort study. J Allergy Clin Immunol. 2017;139(2):597.e4–606.e4.
[9] Elkaim E, Neven B, Bruneau J, et al. Clinical and immunologic phenotype associated with activated phosphoinositide 3-kinase δ syndrome 2: a cohort study. J Allergy Clin Immunol. 2016;138(1):210.e9–218.e9.
[10] Nademi Z, Slatter MA, Dvorak CC, et al. Hematopoietic stem cell transplant in patients with activated PI3K delta syndrome. J Allergy Clin Immunol. 2017;139(3):1046–1049.
[11] Okano T, Imai K, Tsujita Y, et al. Combined immunodeficiency and progressive lymphoproliferative diseases of activated PI3Kδ syndrome rescued by hematopoietic stem cell transplantation. J Allergy Clin Immunol. 2019;143(1):266–275.
[12] Coulter TI, Cant AJ. The treatment of activated PI3Kδ syndrome. Front Immunol. 2018;9:2043.
[13] Durandy A, Kracker S. Increased activation of PI3 kinase-δ predisposes to B-cell lymphoma. Blood. 2020;135(9):638–643.
[14] Maccari ME, Abolhassani H, Aghamohammadi A, et al. Disease evolution and response to rapamycin in activated phosphoinositide 3-kinase δ syndrome: the European Society for Immunodeficiencies-Activated Phosphoinositide 3-Kinase δ Syndrome Registry. Front Immunol. 2018;9:543.
[15] Rao VK, Webster S, Dalm V, et al. Effective "activated PI3Kδ syndrome"-targeted therapy with the PI3Kδ inhibitor leniolisib. Blood. 2017;130(21):2307–2316.
[16] Dimitrova D, Nademi Z, Maccari ME, et al. International retrospective study of allogeneic hematopoietic cell transplantation for activated PI3K-delta syndrome. J Allergy Clin Immunol. 2022;149(1):410.e7–421.e7.
[17] Nakagawa R, Takasawa K, Yeh T-W, et al. Type 1 diabetes mellitus associated with activated phosphatidylinositol 3-kinase delta syndrome, type 2. J Diabetes. 2018;10(5):421–422.