

Hematologic dysregulation as a sign of inborn errors of immunity: activated PI3K δ syndrome (APDS) as a model

Desregulación hematológica como señal de errores congénitos de la inmunidad: síndrome de la fosfatidilinositol-3-cinasa delta activada (APDS) como modelo

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To the Editorial Committee of *Sangre*,

Inborn errors of immunity (IEIs), previously known as primary immunodeficiencies (PIDs), comprise more than 500 predominantly monogenic disorders characterized by multiple clinical signs, including forms of hematologic dysregulation such as benign and malignant lymphoproliferation (LP) and autoimmune cytopenias.¹⁻³

These IEIs include autoimmune lymphoproliferative syndromes (ALPS), caused by abnormalities in the Fas pathway, which account for only a small proportion of autoimmune lymphoproliferative syndromes.² Most cases fall under the term autoimmune lymphoproliferative immune dysregulation (ALPID),² which encompasses a heterogeneous group of conditions with other genetic causes, characterized by chronic or recurrent LP and autoimmune cytopenias, together with other autoimmune signs or increased susceptibility to infections.¹⁻³ Malignant LP, particularly lymphoma, is also common and may be the presenting sign.¹⁻³

Currently, a considerable number of IEI cases involving immune dysregulation and an autoimmune lymphoproliferative phenotype remain without a molecular diagnosis, even after the application of available technologies.² This is due to a lack of clinical suspicion or to their genetic and phenotypic heterogeneity.¹⁻³ It is therefore crucial to raise awareness of the warning signs of hematologic dysregulation that should prompt suspicion and subsequent consultation with clinical immunology.⁴ Genetic testing, such as targeted next-generation sequencing (NGS) panels, should subsequently be considered in selected patients.⁴ In addition, in cases of immune dysregulation, complementary studies such as flow cytometric immunophenotyping, assessment of the expression of key proteins, or functional phosphorylation assays are recommended to support genetic testing or guide decisions while awaiting its results.^{1,4,5} Genetic diagnosis allows the implementation of measures that improve clinical outcomes,⁶ such as close follow-up to facilitate the early detection

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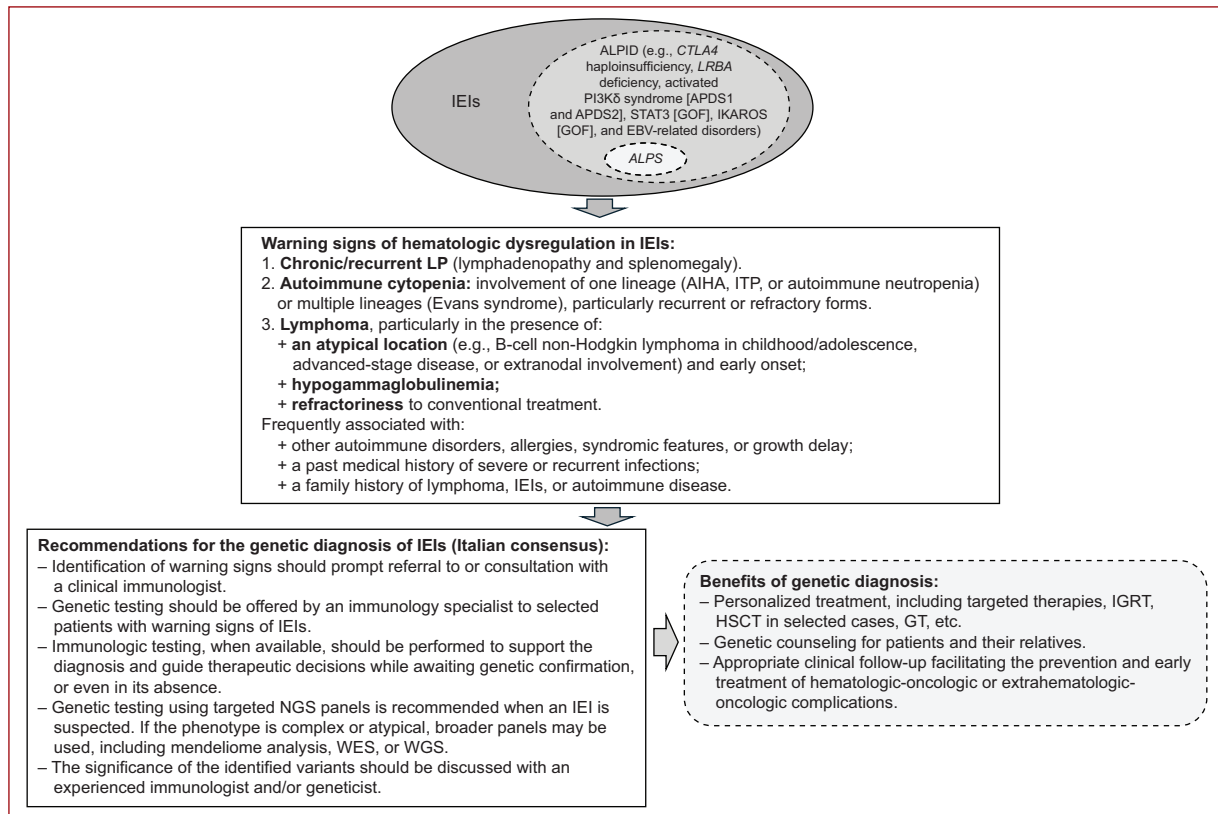


Figure 1. Summary of the warning signs and recommendations for the genetic diagnosis of IELs with an autoimmune lymphoproliferative phenotype (adapted from Bogaert et al.,¹ Magerus et al.,² García-Solís et al.,³ Giardino et al.,⁴ López-Navado et al.,⁵ Forbes et al.,⁶ Vanselow et al.,⁷ Maccari et al.,⁸ Neth et al.,⁹ and Ballow et al.¹⁰).

AIHA: autoimmune hemolytic anemia; ALPID: autoimmune lymphoproliferative immune dysregulation; ALPS: autoimmune lymphoproliferative syndrome; APDS: activated PI3K delta syndrome; EBV: Epstein-Barr virus; IEI: inborn errors of immunity; GOF: gain of function; IGRT: immunoglobulin replacement therapy; LP: lymphoproliferation; NGS: next-generation sequencing; ITP: immune thrombocytopenia; GT: gene therapy; HSCT: hematopoietic stem cell transplantation; WES: whole-exome sequencing; WGS: whole-genome sequencing.

of malignancy or access to targeted treatments.¹⁻³ (Fig. 1).

Activated phosphatidylinositol-3-kinase delta syndrome (APDS) is a paradigmatic example of an IEI caused by genetic variants in genes encoding components of the *PI3Kδ* complex – *PIK3CD* in APDS1 or *PIK3R1* in APDS2 – and is characterized by increased susceptibility to infections, early-onset benign LP, multisystem autoimmunity, and an increased risk of lymphoma. Because of its rarity, progressive nature, and clinical heterogeneity, diagnosis is often delayed for years after symptom onset.^{7,8} This delay is particularly relevant because of the high risk of lymphoma in these patients, approximately 14%,⁸ highlighting the need for early intervention and follow-up. Furthermore, targeted treatments with a significant impact on prognosis are available for these patients.^{8,9} To improve the detection

and management of APDS, a Spanish multidisciplinary consensus was recently developed with the participation of oncohematology specialists (Table 1).⁹ In this consensus, benign LP is presented as a key and frequently initial warning sign of APDS. It is the 2nd most common sign of the syndrome, occurring in approximately 90% of patients after infections, and may present as lymphadenopathy, splenomegaly, and/or hepatomegaly. These signs may be extensive and mimic malignant lymphoma. When APDS is clinically suspected, referral to specialist centers is recommended so that genetic, immunologic, or functional studies of the PI3K-AKT-mTOR pathway, such as AKT and S6 phosphorylation assays, can be performed when appropriate. Once the diagnosis has been confirmed, genetic counseling should be provided to patients and their relatives, and the most appropriate

Table 1. Key recommendations from the Spanish consensus on APDS from an oncohematologic perspective

Variable	APDS consensus recommendations	Specifications
Detection/ warning signs	– APDS is an ultrarare genetic disorder involving immunodeficiency and immune dysregulation, together with an increased risk of lymphoma, and clinically overlaps with other IELs. – APDS is associated with increased susceptibility to recurrent sinopulmonary infections in children; lymphadenopathy, autoimmune cytopenia, and enteropathy are common clinical signs of APDS. – APDS should be considered in the presence of infections, immune dysregulation, and/or lymphoproliferative complications.	Frequency of LP: LP has been identified in 86% of patients with the APDS1 and APDS2 subtypes, whereas lymphoma has been reported in 8% of patients with APDS1 and 23% of those with APDS2. Most common signs of LP in APDS: lymphadenopathy, splenomegaly/hepatomegaly, nodular lymphoid hyperplasia, and EBV-related lymphoma. Causes of increased lymphoma risk: impaired cytotoxic responses, poor control of latent viral infections, or B-cell abnormalities.
Diagnosis	– Early diagnosis of APDS is crucial because it allows appropriate interventions to mitigate disease progression. – The definitive diagnosis of APDS is based on genetic testing. When a novel variant is identified, assessment of its functional impact is recommended in both types of APDS, involving PIK3CD and PIK3R1.	Genetic diagnosis: <i>PIK3CD</i> gain-of-function variants for APDS1; <i>PIK3R1</i> loss-of-function variants for APDS2; and <i>PTEN</i> loss-of-function variants for APDS-L. Functional testing: when a patient presents with clinical features suggestive of APDS, a comprehensive immunologic evaluation should be performed, including measurement of serum immunoglobulins and detailed immunophenotypic analysis. Functional analysis of the PI3K-AKT-mTOR pathway may also help confirm the genetic diagnosis, particularly in the presence of variants of uncertain significance.
Prognosis	– Early onset of clinical signs of LP and infections in APDS suggests a poorer prognosis. – Chronic viral infections are a prognostic factor for lymphoma.	
Treatment	– HSCT, as a potentially curative treatment, may be an option for selected patients, although it is associated with the risks of graft failure, graft-versus-host disease, and infections. – It remains to be established when and how HSCT should be performed and which patients are eligible candidates. – Immunoglobulin replacement therapy should be considered in patients with APDS and hypogammaglobulinemia, recurrent infections, and/or bronchiectasis. – Off-label rapamycin in patients with APDS appears to improve lymphoproliferative signs, such as lymphadenopathy and hepatosplenomegaly, although it is less effective for cytopenia, infection prevention, and gastrointestinal signs. – Off-label rituximab may be used to treat autoimmune cytopenia and non-neoplastic LP, such as lymphadenopathy and hepatosplenomegaly, when rapamycin is ineffective or not tolerated. – Current knowledge of the etiology and pathogenesis of APDS supports the potential use of targeted therapy with selective PI3Kδ inhibitors. – The selective PI3Kδ inhibitor leniolisib improves LP signs, such as splenomegaly, as well as infections and cytopenia. It also normalizes T- and B-cell subsets and is well tolerated.	

(Continues)

Table 1. Key recommendations from the Spanish consensus on APDS from an oncohematologic perspective (*continued*)

Variable	APDS consensus recommendations	Specifications
Follow-up	– Genetic counseling should be offered to all patients with APDS and their relatives because of its autosomal dominant inheritance pattern and high clinical penetrance compared with other IEIs. – Seamless interaction and clearly defined referral pathways should be established between IEI referral centers and other centers to ensure prompt diagnosis, guidance on clinical management, and regular follow-up of APDS.	Prevention of malignant transformation: periodic assessment of lymphoid organs is recommended in all patients with IEIs, particularly those with features of polyclonal LP and an increased risk of malignancy, to enable early identification of clonal development, indicating progression to lymphoma, and the implementation of preventive strategies. Follow-up at referral centers: follow-up at the same center facilitates consistent imaging, pathologic assessments, and monitoring of immune and pulmonary status. This approach enables the early detection of complications and deterioration of affected organs and facilitates reassessment of therapeutic options. Use of functional testing: periodic follow-up using functional assays to assess PI3K-AKT-mTOR pathway activity may complement clinical evaluation of treatment response. Follow-up of targeted treatments (leniolisib): improvements associated with PI3Kδ inhibitors, including improvements in lymphoproliferative complications and phenotypic and functional immunologic abnormalities, may be monitored using imaging techniques such as ultrasonography, computed tomography, and magnetic resonance imaging. Biomarkers are currently under investigation.

APDS: activated PI3K delta syndrome; APDS-L: APDS-like; EBV: Epstein-Barr virus; IEI: inborn error of immunity; GOF: gain of function; LOF: loss of function; LP: lymphoproliferation; HSCT: hematopoietic stem cell transplantation.
 Adapted from Neth et al.⁹

therapeutic option should be determined. Available options include hematopoietic stem cell transplantation, the only potentially curative alternative for selected cases; symptomatic treatments; off-label immunosuppressive agents such as rituximab or sirolimus, an mTOR inhibitor; and novel selective PI3K δ inhibitors such as leniolisib, which targets the underlying cause of APDS and is currently under evaluation by the European Medicines Agency (EMA).

Leniolisib produces early and sustained improvements in LP signs, including reductions in splenic volume and lymphadenopathy, autoimmune cytopenias, and vasculitis. Furthermore, it reduces infections and may even decrease the need for immunoglobulin replacement therapy.⁹ This example illustrates the impact of targeted treatments that may also be applicable to other monogenic IEIs, such as abatacept, CTLA-4-Ig, in *CTLA4* haploinsufficiency or LRBA deficiency, and Janus kinase inhibitors, including tofacitinib and ruxolitinib, in *STAT1* and *STAT3* gain-of-function disorders.¹¹ These treatments require close monitoring. Periodic and structured assessment of lymphoid organs is also necessary because of the risk of progression to lymphoma.^{1-3,7-9}

In summary, increased clinical suspicion of IEIs in the presence of warning signs of hematologic dysregulation is essential and should lead to targeted immunologic evaluation and genetic testing in selected cases within a multidisciplinary approach. This approach not only helps reduce the risk of malignancy but also provides access to targeted treatments, such as leniolisib, that improve patients' quality of life and prognosis. Achieving these objectives will nevertheless require specialized protocols or guidelines and closer coordination among the specialties involved, particularly hematology and immunology.

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Conflicts of interest

O. Neth, L. Alsina, and C. Rodríguez-Gallego have received funding from Pharming. S. Sánchez-Ramón has an ongoing research project and performs consultancy activities for Pharming.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patients' personal data and does not require ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they did not use any form of generative artificial intelligence in the writing of this manuscript.

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