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Primary immunodeficiency and autoimmunity: A comprehensive review

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ABSTRACT

The primary immunodeficiency diseases (PIDs) include many genetic disorders that affect different components of the innate and adaptive responses. The number of distinct genetic PIDs has increased exponentially with improved methods of detection and advanced laboratory methodology. Patients with PIDs have an increased susceptibility to infectious diseases and non-infectious complications including allergies, malignancies and autoimmune diseases (ADs), the latter being the first manifestation of PIDs in several cases. There are two types of PIDS. Monogenic immunodeficiencies due to mutations in genes involved in immunological tolerance that increase the predisposition to develop autoimmunity including polyautoimmunity, and polygenic immunodeficiencies characterized by a heterogeneous clinical presentation that can be explained by a complex pathophysiology and which may have a multifactorial etiology. The high prevalence of ADs in PIDs demonstrates the intricate relationships between the mechanisms of these two conditions. Defects in central and peripheral tolerance, including mutations in *AIRE* and T regulatory cells respectively, are thought to be crucial in the development of ADs in these patients. In fact, pathology that leads to PID often also impacts the Treg/Th17 balance that may ease the appearance of a proinflammatory environment, increasing the odds for the development of autoimmunity. Furthermore, the influence of chronic and recurrent infections through molecular mimicry, bystander activation and super antigens activation are supposed to be pivotal for the development of autoimmunity. These multiple mechanisms are associated with diverse clinical subphenotypes that hinders an accurate diagnosis in clinical settings, and in some cases, may delay the selection of suitable pharmacological therapies. Herein, a comprehensively appraisal of the common mechanisms among these conditions, together with clinical pearls for treatment and diagnosis is presented.

1. Introduction

The primary immunodeficiency diseases (PIDs) include several genetic anomalies that affect different components of the innate and adaptive responses [1]. ADs include a heterogeneous group of disorders of the immune system secondary to a loss of tolerance to self-antigens that may be organ specific or systemic [1]. Initially, PIDs and ADs were considered independent, or even polar opposites. However, due to genetic advances and a greater understanding of the pathophysiological processes involving T-cell development, immune tolerance, T-cell signaling, complement pathway and inflammation, they are now accepted as interconnected processes, sharing some common mechanisms [1].

The first description of PIDs appeared in 1952 when Ogden Bruton discovered an X-linked agammaglobulinemia (XLA). XLA is caused by a mutation in the Bruton tyrosine kinase gene (BTK) characterized by the presence of recurrent infections in respiratory and gastrointestinal tracts. Since then, more than 350 unique immunodeficiency diseases have been identified [2]. Of these, selective immunoglobulin IgA deficiency (SIgAD) is the most frequent in children and adults, and the one which is more frequently associated with ADs [3].

Although PIDs can affect both adults and children, they are more common during childhood. The distribution and prevalence of PIDs varies between populations. Countries such as Iran, Australia, France, United States, Europe, and 12 Latin American countries have created national registries in order to identify the epidemiological distribution of these diseases. The French national registry center (CEREDIH) reported a prevalence of 4.4 patients per 100,000 inhabitants [4], and data from the United States estimated a prevalence of 1/1200 people,

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Abbreviations

AAD	Autoimmune Addison disease
ACPA	*Anti*-citrullinated protein antibodies
ADs	Autoimmune diseases
AE	Autoimmune encephalitis
AGA	Anti-gliadin antibodies
AHP	Autoimmune hypoparathyroidism
AIE	Autoimmune enteropathy
AIH	Autoimmune hepatitis
AIHA	Autoimmune hemolytic anemia
AIL:	Autoimmune leukopenia
AIP	Autoimmune pancreatitis
AIRE	Autoimmune regulator
AIE	Autoimmune enteropathy
AIT	Autoimmune thrombocytopenia
AITD	Autoimmune thyroid disease
ALPS	Autoimmune lymphoproliferative syndrome
ALT	Alanine aminotransferase
APECED	Autoimmune polyendocrinopathy, candidiasis ecto-dermal, dystrophy
APGS	Autoimmune polyglandular syndrome
APRIL:	A proliferation inducing ligand
APS	Antiphospholipid syndrome
AS	Ankylosing spondylitis
AST	Aspartate transaminase
A-T:	Ataxia telangiectasia
ATM	ATM serine/threonine kinase
AZA	Azathioprine
BAFF	B-cell activating factor
BCR	B-cell receptor
BTK	Bruton tyrosine kinase
CASP	Caspase
CaSR	Calcium-Sensing Receptor
CD	Celiac disease
CGD	Chronic granulomatous disease
CLT	Chronic lymphocytic thyroiditis
CMC	Chronic mucocutaneous candidiasis
CTLA4	Cytotoxic T-lymphocyte associated protein 4
CVID	Common Variable Immunodeficiency
DGS	DiGeorge syndrome
DL:	Discoid lupus
DMARDs	Disease-modifying antirheumatic drugs
DOCK8	Dedicator of cytokinesis 8
EBV	Epstein-Barr virus
EMA	Endomysial antibody assay
ES	Evan's syndrome
ESR	Erythrosedimentation rate
FASL:	FAS ligand
FOXP3	Forkhead box P3
GAD65	Glutamic acid decarboxylase antibodies
GD	Graves' disease
GLILD	Granulomatous-lymphocytic interstitial lung
HAE	hereditary angioedema
HIES	Hyper-IgE syndrome
HIGM	Hyper- IgM syndrome
HLH	Hemophagocytic lymphohistiocytosis
HT	Hashimoto's thyroiditis
HSCT	Hematopoietic stem cell transplantation
IAA	Insulin autoantibodies
IA2	Protein tyrosine phosphatase antibodies
IBD	Inflammatory bowel disease
IFNωAbs	Interferon-omega autoantibodies
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked
IRT	Immunoglobulin G replacement therapy
ITP	Immune thrombocytopenic purpura
IVIg	Intravenous gamma globulin infusions
JDM	Juvenile dermatomyositis
JIA	Juvenile idiopathic arthritis
JMF	Jeffrey Modell Foundation
LRBA	Lipopolysaccharide responsive beige-like anchor
LoS	Localized scleroderma
MG	Myasthenia gravis
MHC	Major histocompatibility complex
MMF	Mycophenolate mofetil
mTOR	Mammalian target of rapamycin
MTX	Methotrexate
NALP5Ab	NACHT leucine-rich-repeat protein 5 autoantibodies
NSAIDs	Nonsteroidal anti-inflammatory drugs
NADPH	Nicotinamide adenine dinucleotide phosphate
OS	Omenn syndrome
PA	Pernicious anemia
PBC	Primary biliary cholangitis
PID	Primary immunodeficiency
PolyA	polyautoimmunity
PSO	Psoriasis
RA	Rheumatoid arthritis
RAG	Recombination-activating gene
ROS	Reactive oxygen species
RP	Raynaud's phenomenon
STAT	Signal transducers and activators of transcription
SIgAD	Selective immunoglobulin IgA deficiency
SLE	Systemic lupus erythematosus
SS	Sjögren's syndrome
T1D	Type 1 diabetes
TCR	T-cell receptor
TLR	Toll-like receptor
tTG	Tissue Transglutaminase antibody
TPO	*Anti*-thyroperoxidase antibodies
TRAb	Thyroid-stimulating hormone receptor
21-OHAbs	21- hydroxylase autoantibodies
U	Uveitis
UC	Ulcerative colitis
VATS	Video-assisted thoracoscopic
Vcr	Vincristine.
Vbl	Vinblastine.
VIT	Vitiligo
WAS	Wiskott-Aldrich syndrome
WASp:	Wiskott-Aldrich syndrome protein
XLA	X-linked agammaglobulinemia
XLP	X-linked lymphoproliferative disease

which represents the highest prevalence worldwide [5]. In Europe, the European Society for Immunodeficiencies (ESID) registry identified 28,000 patients from more than 125 medical centers. To date, it is considered the largest database of patients suffering from PIDs [6]. The Latin American Group for Primary Immunodeficiency Diseases (LAGID) reports that out of 3321 patients, 53.2% have antibody deficiencies [7]. In underdeveloped countries, information is scarce due to lack of knowledge about these diseases, delayed diagnosis, and underreporting [8].

Patients with PIDs have an increased susceptibility to infectious diseases caused by either intracellular or encapsulated agents [2]. These patients may also be more susceptible to ADs, allergic diseases and malignancies [9]. Immunodeficiencies can be classified into two groups: 1) monogenic immunodeficiencies due to mutations in genes

that may also be involved in immunological tolerance [10], or 2) polygenic immunodeficiencies characterized by a heterogeneous clinical presentation explained by a greater complexity in the immune signaling pathways [10,11].

Genetic analysis has made it possible to establish associations between PIDs and ADs, since different mutations in PID genes are implicated in the development of diseases, such as *BTK* (Bruton tyrosine kinase) in X-linked agammaglobulinemia [12], *FOXP3* (forkhead box P3) in X-linked Immune dysregulation polyendocrinopathy-enteropathy [13], the autoimmune regulator (*AIRE*) in autoimmune polyendocrinopathy, candidiasis ectodermal dystrophy [14], *ATM* (ATM serine/threonine kinase) in ataxia-telangiectasia (A-T) [15], lipopolysaccharide responsive beige-like anchor *LRBA* [16], *CTLA4* (cytotoxic T-lymphocyte associated protein 4) [17], *FAS, FASL* [18], *WASp* in Wiskott-Aldrich syndrome [19], and *STAT or STIM1* [20]. These are some of the more well studied genetic immunodeficiencies. This suggests that PIDs and ADs can, in most cases, be grouped in the same spectrum of illness [1]. Because the genetic mutations may affect the activity of multiple cell types or signaling molecules, PIDs and ADs can in fact present with a clinical presentation that is not exclusively one or the other.

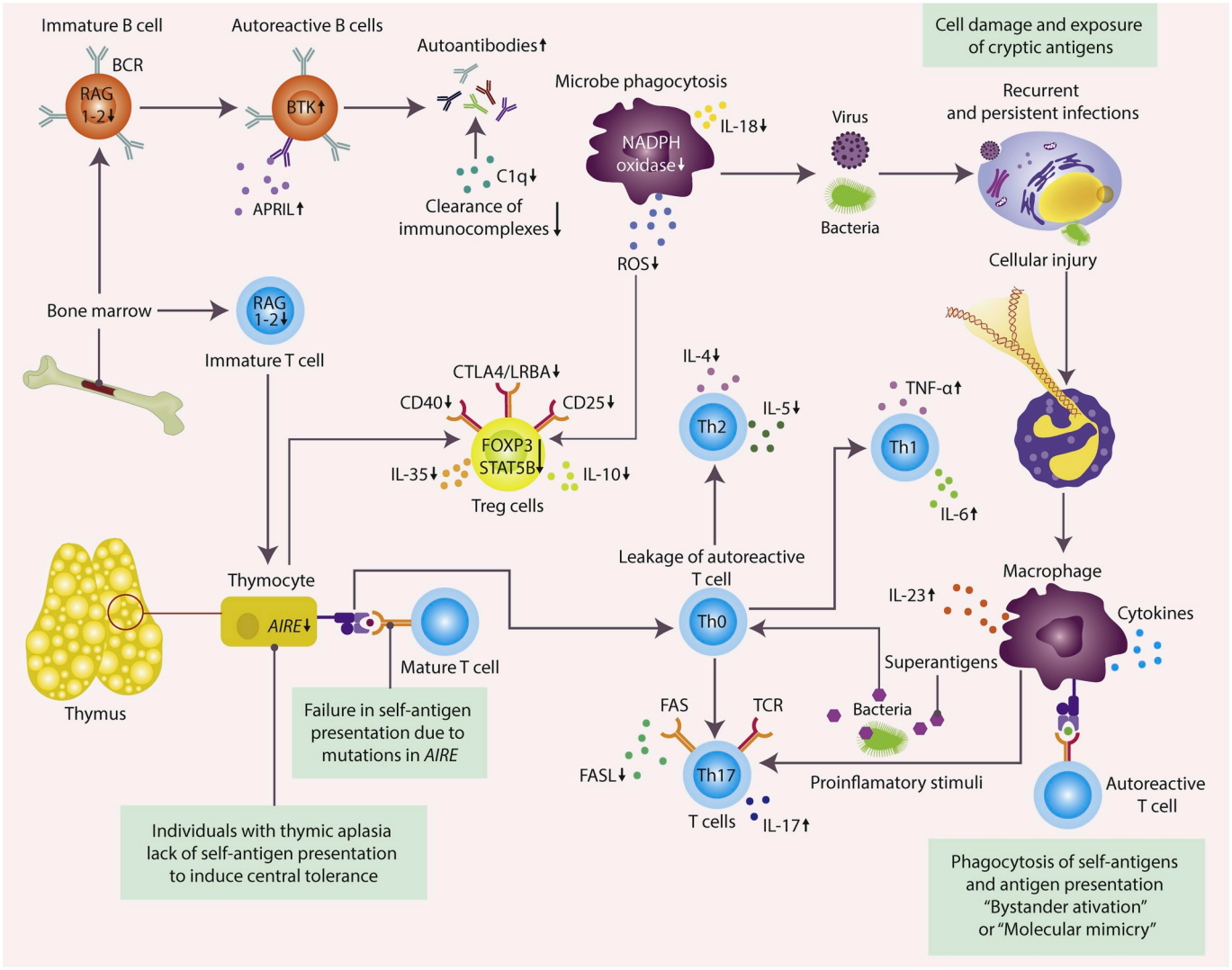

Fig. 1. Immunological mechanisms associated with autoimmunity in patients with PIDs. In the thymus, AIRE deficiency impairs self-antigen presentation, which hinders negative selection of autoreactive T-cells. This produces leakage of reactive T cells that further differentiate into Th1, Th2, and Th17 subsets which produce proinflammatory cytokines such as IL-6, IL-17, and TNF-α, whereas regulatory cytokines such as IL4 and IL-5 are usually reduced. In this scenario, other mutations in RAG 1 and 2 are associated with incomplete negative selection of autoreactive T and B cells. Since individuals with PIDs exhibit a high burden of infectious diseases, four scenarios for autoimmunity could take place: 1) infectious agents may share similarities with human proteome initiating a phenomenon of cross-reactivity, 2) infectious diseases induce cell damage and exposure of "cryptic antigens" which ultimately will be presented by macrophages to autoreactive T cells, 3) frequent and recurrent infectious diseases induce an over production of proinflammatory cytokines such as IL-23 which help to differentiate autoreactive T cell subsets (e.g., Th17), and 4) superantigens produced by infectious agents can induce activation of autoreactive T cells. On the other hand, Treg cells can exhibit several defects that impair its role in peripheral tolerance. Reduced production of production of ROS by macrophages, secondary to malfunction in the NADPH oxidase, decreases the activation of regulatory T cells. Furthermore, Tregs require activation by CD25, which is essential for their growth and survival, and mutations in this receptor are though to impair their peripheral regulatory function. Other mutations in CTLA4/LRBA and CD40, together with a reduce production IL-35 and IL-10, may also impair the inhibitory function of Tregs. Mutations in *BTK* are associated with an increased survival of autoreactive B cells, which produce a high number of autoantibodies. In addition, these B cells could also be activated by high levels of APRIL and BAFF. Lastly, some subjects with complement deficiencies may show defects in clearance of immune complexes which may result from autoimmune phenomena. AIRE: autoimmune regulator; APRIL: A proliferation-inducing ligand; BAFF: B cell activating factor; BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; CTLA4: cytotoxic T-lymphocyte associated protein 4; FOXP3: forkhead box P3; LRBA: lipopolysaccharide responsive beige-like anchor; NADPH: nicotinamide adenine dinucleotide phosphate; PIDs: primary immunodeficiencies; RAG: recombination activating gene; ROS: reactive oxygen species; STAT: signal transducers and activators of transcription TCR: T-cell receptor.

2. Autoimmunity and primary immunodeficiencies: the missing link

Although the simultaneous appearance of PIDs and ADs is at first glance, counter intuitive, the high prevalence of ADs in immunodeficiencies has increased the suspicion of the presence of common mechanisms [10]. Defects in central and peripheral tolerance, together with the presence of autoreactive T and B cells are common features of both diseases [1]. Furthermore, common genetic risk factors for PIDs and ADs have been described [1], and recurrent infections in patients with PIDs may influence the appearance of ADs (Fig. 1) [21].

Although ADs differ phenotypically and have different diagnostic criteria, their physiopathological mechanisms are similar (i.e., autoimmune tautology). In clinical practice, exist two conditions supporting this assumption: polyautoimmunity (PolyA) and familial autoimmunity (FAI). PolyA is the presence of two or more ADs in a single patient whereas FAI occurs when different relatives from a nuclear family present with diverse ADs [22]. The latter suggests that inherited genes are essential for the development of ADs, specially PolyA. For instance, Sjogren's syndrome (SS) and autoimmune thyroid disease (AITD) share common *HLA* susceptibility alleles (i.e., *HLA-DPB1, HLA-DQA1, HLA-DRB1, HLA-DQB1*) that may explain their simultaneous appearance in a single patient [23], or members of the same family [24]. This advocates for a similar phenomenon in PIDs, since genetic burden in these diseases may explain the appearance of similar traits in families, including autoimmune conditions that resembles PolyA [10], supporting the notion of common mechanisms between immunodeficiencies and autoimmunity.

Patients with PIDs exhibit mutations in genes considered to be important in the development of immunological tolerance (Fig. 2). *AIRE* is responsible for the expression of autoantigens, and selection of autoreactive T cells in the thymus [25]. Mutations in *AIRE* have been associated with the appearance of autoimmune polyendocrinopathy, candidiasis ectodermal, dystrophy (APECED) [25], and Omenn syndrome (OS) [26] (Table 1). Patients with thymic aplasia are thought to exhibit defects in central tolerance due to the lack of expression of this gene [27]. Malfunction in *AIRE* may impair the clearance of autoreactive T cells in the thymus [1,25] as well as the development of Treg cells [26].

Rearrangement of T- and B-cell receptors is crucial for immune system development [28]. This process relies on the *RAG1* and *RAG2* genes which are critical for Variable (V) Diversity (D) Joining (J) recombination [29]. Mutations in these two genes are associated with incomplete negative selection of autoreactive T cells in the thymus [30] which helps explain how these patients with PIDs can also present with ADs.

Leakage of autoreactive T cells in central tolerance may explain the deleterious effect of infectious diseases on autoimmunity via several mechanisms [21]. One of them is molecular mimicry (i.e. similarity between antigens from pathogens and the human structures) [21]. Recurrent infections exhibit by patients with PIDs involve autoreactive T cells being activated by different pathogens that share similarities with the human proteome leading to autoimmunity, a phenomenon known as cross-reactivity (Fig. 1). In addition, infectious diseases may induce the production of cellular debris which can be presented to autoreactive T cells, a process known as “bystander activation” [31]. Furthermore, superantigens are a class of antigens that produces a non-specific activation of T cells that results in polyclonal T-cell activation and cytokine production [32]. These compounds have the unique ability to cross-link several T cell receptors and thus activate many different antigenic specificities synchronously [33,34]. Staphylococcus and mycoplasma are examples of superantigen activity, and they are considered the most common infectious agents found in patients with PIDs [35,36]. Thus, lack of central and peripheral tolerance to control these external agents may help explain the simultaneous appearance of PIDs and ADs in the scenario of multiple and recurrent infections (Fig. 1).

Some individuals show a lack of CD25 expression which is considered chief for the development of Treg cells [37]. Note that Treg defects are not exclusive to patients with CD25 deficiency. Patients with APECED show a low expression of Forkhead box protein P3 (FOXP3) which is critical for Treg cell activation and proliferation [27,38]. In DiGeorge syndrome (DGS) thymic abnormality impairs the production of $CD4^+$ $CD25^{+high}$ T cells [27]. Concomitantly, these patients show a severe reduction in Treg cells, low IL-10 levels from $CD4^+$ T cells [39], with high levels of IL-17, IL-6, and IL-23 [40]. This suggests that individuals with Treg deficits have a high burden of cellular and inflammatory stimuli. In addition, a mutation in the Wiskott-Aldrich syndrome protein (WASp) associated with low regulatory cells and high proinflammatory cytokine production (i.e., Th17) has also been implicated in a low expression of T and B regulatory cells (Table 2) [41].

LRBA is associated with multiple processes such as signal transduction, regulation of transcription, assembly of cytoskeleton, chromatin dynamics, and apoptosis in immune cells including Tregs [42]. Interestingly, LRBA is associated with CTLA-4, the latter being responsible for regulating peripheral tolerance by inhibiting the

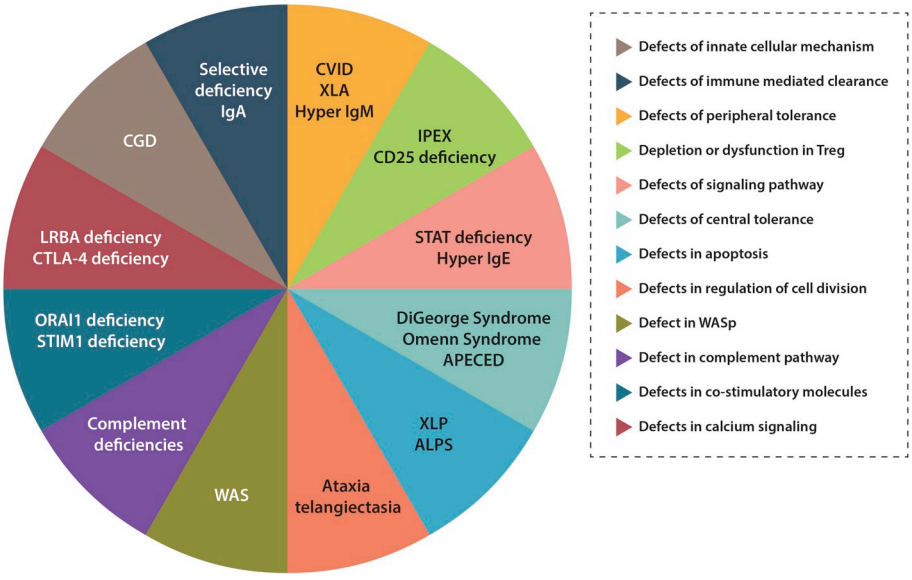

Fig. 2. Immunological defects associated with the development of PIDs. APECED: autoimmune polyendocrinopathy, candidiasis ectodermal, dystrophy syndrome; ALPS: autoimmune Lymphoproliferative Syndrome; CGD: chronic granulomatous disease; CVID: common variable immunodeficiency; IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PIDs: primary immunodeficiencies; WAS: Wiskott-Aldrich syndrome; WASp: Wiskott-Aldrich syndrome protein. XLA: X-linked agammaglobulinemia; XLP: X-linked lymphoproliferative disease.

Table 1
Association of primary immunodeficiency, genetic defects, and autoimmune diseases.

PID	Genetic defect	Associated ADs	References
XLA	*BTK*	JIA, RA, IBD, T1D, autoimmune cytopenias.	[47,72–76]
APECED	*AIRE*	AHP, HT, GD, PBC, T1D, AIH, VIT, PSO.	[82–89]
Omenn Syndrome	*RAG1, RAG2*	HT, IBD, ITP.	[92,93]
DGS	Chromosome 22q11 deletion	ITP, AIHA, HT, GD, IBD, Uveitis, and JIA.	[103–107,111–114]
IPEX	*FOXP3*	AIE, T1D, autoimmune cytopenias, HT, and eczema.	[122,125–128]
Selective IgA deficiency	Unknown	AIJ, RA, ITP, AHA, IBD, SS, SLE, CD, VIT, and T1D.	[140–142,145–149]
LRBA deficiency	*LRBA*	GLILD, autoimmune cytopenias, HT, T1D, IBD, SLE, AITD, and JIA.	[155–159,161–163]
CVID	*TACI, BAFF-R, MSH5*	AIHA, ITP, PA, SLE, JIA, RA, T1D, HT, SS, IBD, and VIT.	[174–183]
CGD	gp91phox, p22phox, p47phox, p67phox, p40phox	SLE, IBD ITP, T1D, JIA, RA, APS.	[193,197–205]
XLP	*SH2D1A, XIAP*	HLH	[214]

Abbreviations: ADs: Autoimmune diseases; AHP: autoimmune Hypoparathyroidism; AIE: Autoimmune enteropathy; AIHA: autoimmune hemolytic anemia; AIH: autoimmune hepatitis; AIN: autoimmune neutropenia; CD: celiac disease; CGD: Chronic granulomatous disease; CVID: Common Variable Immunodeficiency; DGS: DiGeorge syndrome; DL: discoid lupus; GD: Graves' disease; GLILD: Granulomatous-lymphocytic interstitial lung; HT: Hashimoto's thyroiditis; HLH: Hemophagocytic lymphohistiocytosis; IBD: inflammatory bowel disease; ITP: immune thrombocytopenic purpura; JIA: juvenile idiopathic arthritis; MG: myasthenia gravis; PA: pernicious anemia; PBC: primary biliary cholangitis; PID: primary immunodeficiency; PSO: psoriasis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; T1D: type 1 diabetes; VIT: vitiligo; XLA: X-linked agammaglobulinemia; XLP: x-linked lymphoproliferative disease; AITD: autoimmune thyroid disease.

activation of T lymphocytes through negative signaling, competitive inhibition of the CD28, or elimination of ligands from antigen-presenting cells [43]. Since these two molecules work together at the level of cellular functions, they appear to be pivotal for peripheral tolerance [42]. Furthermore, as some patients show mutations in these genes, it is possible that a failure in the functioning of Tregs may explain the ineffective control of autoreactive cells in patients with PIDs. Thus, either a reduced number of Tregs or a failure of these cells to function in peripheral tissues may increase the odds of having an ADs. Mutations in *LBRA* have been reported as a genetic defect in some patients with common variable immunodeficiency (CVID).

Macrophage phagocytosis impairment secondary to NADPH oxidase deficiency may present as PID. In addition to its bactericidal activity, this enzyme is critical for the production of reactive oxygen species (ROS) which are required to activate Treg cells [44]. Other factors such as STAT5B appear to be critical for Treg cell activation, and some patients with PIDs exhibit malfunction in these signaling pathways [45]. Treg cells appear play a central role in the development of autoimmunity in PIDs.

Over activation of T and B cells secondary to mutations in signaling pathways, in turn, has been recently described in patients with PIDs. For example, B cells show mutations in the *BTK* gene which is crucial for their intracellular signaling [46]. *BTK* mutations are associated with the appearance of autoimmunity due to an enhanced maturation and survival of autoreactive B cells with an increased production of autoantibodies [47]. While this is counterintuitive, the overproduction of autoantibodies seen in other humoral immunodeficiencies such as Hyper IGM syndrome is more understandable [48]. Other mechanisms are associated with over activation of B cells. In some PIDs, such as CVID, patients show high levels of proliferation inducing ligand (APRIL) and B cell activating factor (BAFF) [49]. Both factors promote the proliferation and survival of B cells and have recently been related to systemic ADs such as RA and systemic lupus erythematosus (SLE) [50–53], including an enhanced production of autoantibodies such as anti-double-stranded DNA (*anti*-dsDNA) antibodies in SLE, *anti*-SSA/Ro antibodies in SS, and rheumatoid factor (RF) in RA suggesting the role in activation and production of antibodies in ADs [54]. In addition, mutations in FASL/FAS give rise to defective apoptosis of lymphocytes, which causes an alteration in immune homeostasis with the resulting accumulation of autoreactive T and B cells in patients with PIDs [55,56].

IL-10-producing regulatory B cells in CVID were reduced when comparing with healthy controls, thus suggesting that lack of peripheral autoreactive B− and T-cells immunomodulation may have some influence in the appearance of CVID, and probably ADs [57]. However, in selective IgM deficiency, levels of Breg and $CD8^+$ Treg cells were paradoxically increased [58]. Although the regulatory role of Breg cells on Tregs and anti-self B cells has been recently reported [59], their function in most of PIDs is still unclear. Further analyses in these cells may allow the identification of new pathways to uncover the mechanisms associated to PID and autoimmunity.

A lack of complement proteins for clearance of immunocomplexes [60–63], CD40 deficiency [64], and mutations of the *JAK-STAT* and *DOCK8* genes that affect B− and T-cell development [65] are thought to play a key role in the development of autoimmunity in individuals with PIDs. However, their mechanisms and the magnitude of their influence are not fully understood.

Table 2
Association of primary immunodeficiency, genetic defects, and autoimmune diseases.

PID	Genetic defect	Associated ADs	References
WAS	*WASp*	AIN, ITP, AIHA, RA, JIA and IBD.	[218–222]
ALPS	*FAS, FAS* ligand, caspase 8 and 10, *MAGT1, STAT3, and TNFAIP3*	ITP, AIHA, SLE, RA, and JIA.	[17,226,227]
Complement deficiencies	C1q, C1r, C1s, C4, C2	SLE, JIA, DM, RA.	[228–230]
Hyper- IgM syndrome	*CD40 L/CD40, UNG, NEMO, IkBα.*	AIHA, ITP, IBD, T1D, discoid lupus.	[232–236]
Hyper-IgE syndrome	*STAT3, DOCK8*	RA, ITP, SLE, bullous pemphigoid, and JDM.	[241–246]
Ataxia- telangiectasia	*ATM*	HT, JIA, ITP, and AIHA.	[249–252]
STAT deficiency	*STAT1, STAT3, STAT5B*	AIHA, AITD, CD, T1D, PSO, and alopecia.	[258,259,261,262]
ORAI1 deficiency	*ORAI1*	ITP and AIHA	[268]
STIM1 deficiency	*STIM1*	ITP and AIHA	[268]
CD25 deficiency	*CD25*	T1D, AITD, ITP, AIHA, and bullous pemphigoid.	[37]

Abbreviations: WAS: Wiskott-Aldrich syndrome; ALPS: Autoimmune Lymphoproliferative syndrome; AIN: autoimmune neutropenia; ITP: immune thrombocytopenic purpura; AIHA: autoimmune hemolytic anemia; RA: rheumatoid arthritis; JIA: juvenile idiopathic arthritis; IBD: inflammatory bowel disease; SLE: systemic lupus erythematosus; DM: dermatomyositis; T1D: type 1 diabetes; JDM: juvenile dermatomyositis; HT: Hashimoto's thyroiditis; CD: celiac disease; PSO: psoriasis; AITD: autoimmune thyroid disease.

In summary, peripheral and central tolerance defects are crucial for the development of autoimmunity in patients with PIDs, together with over activation of T and B cells, and chronic or recurrent infections.

3. Autoimmune diseases in primary immunodeficiencies

Most patients with PIDs are underdiagnosed due to a lack of knowledge about clinical manifestations, mechanisms implicated in the development of the disease, and limitations in the immunological diagnosis. The Jeffrey Modell Foundation (JMF) listed 10 warning signs that may help to identify those patients who are likely to have PIDs. If the patient exhibits two or more of the following signs, physicians should refer these individuals to an immunologist: 1) “eight or more ear infections within 1 year,” 2) “two or more severe sinus infections within a year,” 3) “two or more months on antibiotics with a poor response,” 4) “two or more episodes of pneumonia within 1 year,” 5) “failure of an infant to gain weight or grow normally”, 6) “recurrent, deep skin or organ abscesses” 7) “persistent thrush in the mouth or fungal infection on the skin,” 8) “need for intravenous antibiotics to eradicate infections,” 9) “two or more systemic infections,” and 10) “the presence of a family history of PIDs” [66]. We suggest that an additional criterion should be added to the warning signs, namely “presence of autoimmune manifestations” (Fig. 3). This new warning sign may help raise physicians' awareness of autoimmunity in PID and improve their assessment of these patients.

Autoimmunity may be the first manifestation of immunodeficiency and may be present during the course of PID. The prevalence of ADs in patients with selective IgA deficiency is about 36% [67]. In CVID, autoimmunity occurs in 20–30% of patients with a high frequency of autoimmune cytopenias [68]. In Wiskott-Aldrich syndrome (WAS), autoimmune conditions have been documented in up to 25% of the patients [69], with most of them presenting with immune thrombocytopenic purpura (ITP) and neutropenia (40%) [70]. Although these frequencies suggest the simultaneous appearance of PIDs and ADs, the prevalence as well as the description of ADs in other PIDs is not well defined. Thus, a focused systematic review was done including those studies reporting coexistence of PIDs and ADs in Pubmed, Embase, and Lilacs (supplementary material 1). The most relevant reports are shown and discussed below.

3.1. X-linked agammaglobulinemia (XLA)

The X-linked agammaglobulinemia (XLA) was described in 1952 by the American pediatrician Ogden Bruton as a genetic defect with an inheritance pattern linked to the X chromosome. It is caused by a mutation in the *BTK* gene [46]. In addition to its role in B cell development, this gene is associated with the Toll-like receptor (TLR) pathway, which is part of the innate immune system responsible for the identification of pathogens and the consequent activation of the immune response [71]. Patients with XLA can present with recurrent infections such as pneumonia, otitis, sinusitis, conjunctivitis, and chronic diarrhea, progressing to serious and life-threatening infections in some cases.

Inflammatory bowel disease (IBD) is one of the most common gastrointestinal manifestations in XLA. As reported by Barmettler et al. [72], about 35% of XLA patients developed gastrointestinal manifestations, and up to 10% reported IBD. In addition, in the classic case report of Robbins et al. [73], a patient with XLA developed autoimmune hemolytic anemia (AIHA) which was also found in his first degree relatives. Vancsa et al. [74] found that non-identical twins had a mutation in exon 12 in the *BTK* gene associated with recurrent infections and a low B-cell count, and Patiroglu et al. [75] found that two siblings had a

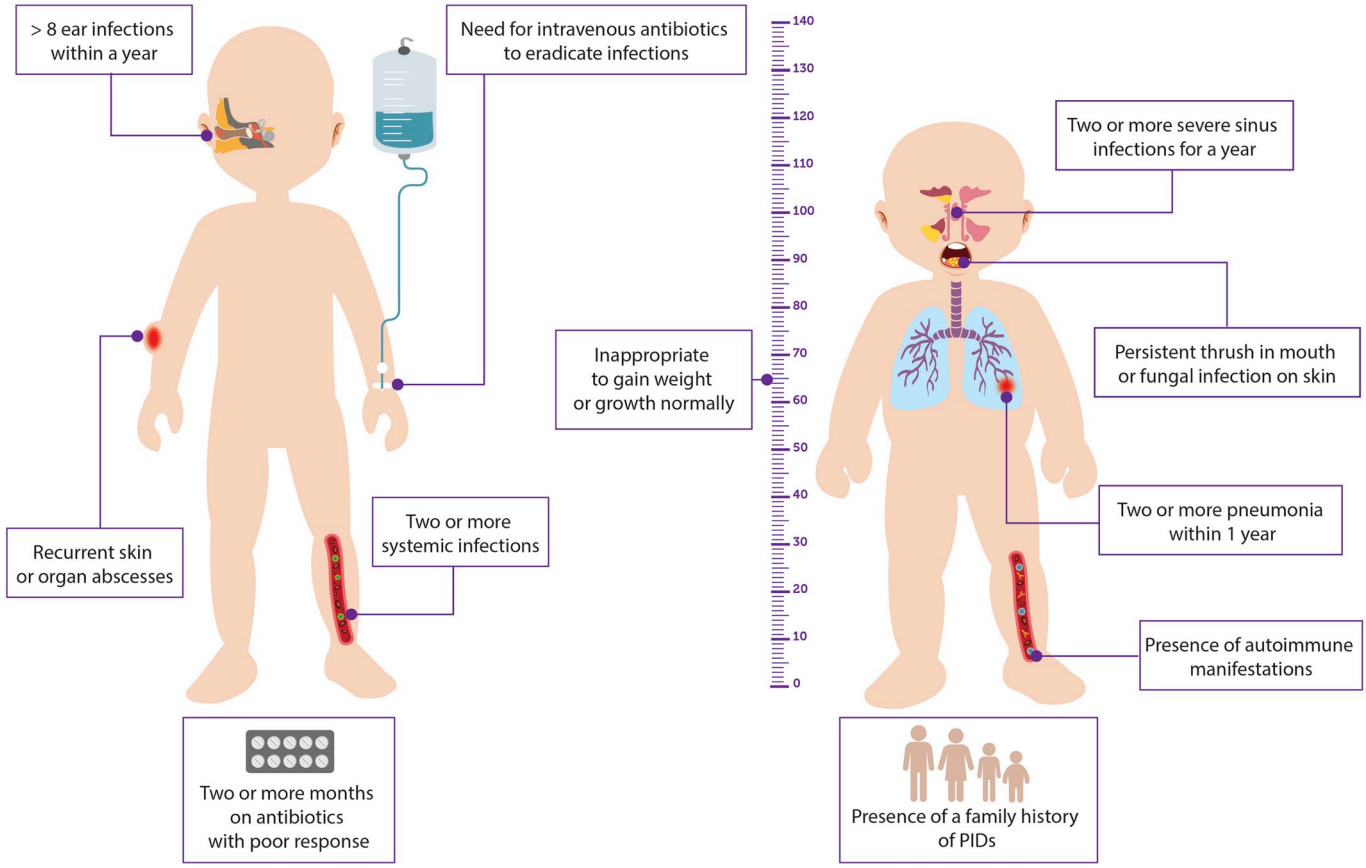

Fig. 3. The Jeffrey Modell Foundation warning signs for primary immunodeficiencies. The inclusion of autoimmunity as an additional criterion may help to improve diagnosis and follow up of comorbidities associated with these diseases.

previously undescribed new mutation in exon 15 in *BTK*. Both reports were associated with juvenile idiopathic arthritis (JIA).

In the study done by Nyhoff et al. [76], BTK-deficient K/BxN mice showed protection for the development of RA. Authors suggested that protection was conferred by a defect in the B-cell signaling pathways that may had shortened the half-life of autoreactive B cells. In this sense, Bonami et al. [47] found that anergic and autoreactive B cells rely on BTK-mediated signaling for maturation and survival in murine models of type 1 diabetes (T1D). A further finding was that mutations in *BTK* reduced insulin binders in the marginal and follicular zone of B cells as well as the numbers of Peyer's patch, which are essential for production of IgA. Their data suggested that patients with mutations in these genes may exhibit alterations in the B-cell signaling that can be associated with the development of autoimmunity via the survival of autoreactive B cells.

3.2. Autoimmune polyendocrinopathy, candidiasis ectodermal, dystrophy (APECED)

APECED or autoimmune polyendocrine syndrome type 1 (APS-1) has an autosomal recessive inheritance pattern caused by a mutation in *AIRE* gene [25]. More than 100 mutations in AIRE have been described in different populations which could explain the varied clinical spectrum of the disease and its association with various ADs. The most frequent mutations that have been identified are R257× in exon 6 and the L323SfsX51 present in 95% of the patients with APECED [77].

The epidemiological data varies across populations. There is a low prevalence of the disease in the Japanese population (i.e.,1:10,000,000), whereas in Iranian Jews, it reaches a prevalence of 1:9000 [78]. Sardinians have an estimated prevalence of 1:14,000 [79], and Norway has reported a prevalence of around 1:9000 inhabitants [80]. APECED presents with a classical triad of signs and symptoms (i.e., primary adrenocortical insufficiency, hypoparathyroidism, and chronic mucocutaneous candidiasis-CMC). However, to make the diagnosis, the presence of at least two out of three conditions is mandatory. Although the first manifestation of CMC usually appears during the first five years, other manifestations of the syndrome may not appear until the fourth decade of life [81].

Patients with this syndrome may show systemic autoimmune compromise characterized by vitiligo, hypothyroidism, and rheumatoid factor positive arthritis [82]. García-Lozano et al. [83] found that some polymorphisms in this gene were associated with the development of RA (i.e., rs878081C). In the meta-analysis of Bérczi et al. [84], the polymorphisms rs2075876 and rs760426 in *AIRE* were associated with a higher risk for RA, predominantly in Asian populations. Whether these polymorphisms may explain the coexistence of APECED and RA is still unknown. Nevertheless, it is likely that the defects in central tolerance shared by these two conditions result in the synchronous appearance in a single patient.

In 2008, Perniola et al. [85] studied a group of Apulian patients with APECED and documented a high prevalence of Hashimoto's thyroiditis (HT) (50%), suggesting that *AIRE* mutations may play a role in endocrinological manifestations. However, in the study done by Colobran et al. [86], Graves' disease (GD) was not associated with *AIRE* genetic variants. This was probably due to methodological issues and a lack of statistical power. Further studies to evaluate the genetic factors associated with the epidemiological link between APECED and thyroid autoimmunity are needed.

T1D is typically described in Finnish APECED patients compared to European, Irish, or Arab families [87,88]. The minisatellite DNA polymorphism consisting of a variable number of tandem repeats (VNTR) at the human insulin gene (*INS*) 5′-flanking region (known as IDDM2) has demonstrated allelic effects on insulin gene transcription *in vitro* and has been associated with the level of insulin gene expression *in vivo*. In 50 Finnish patients with APECED, Paquette et al. [89] found that IDDM2 was more common in patients than in controls, and that having two short alleles conferred a 43.5-fold increased risk. In another study, *AIRE* mutations did not influence diabetic phenotype in APECED patients, but HLA class II alleles appeared to be determinant (i.e., HLA-DRB1*15-DQB1*0602) [90]. These data suggest that autoimmune pathology in the pancreas of patients with APECED is determined by a complex interaction between *HLA* and non-*HLA* genes. Laakso et al. [38] found that patients with APECED exhibit a regulatory T-cell defect associated with low FOXP3 expression as well as impaired peripheral Treg cell activation. The autoimmune phenomena found in APECED is likely a result of defects in peripheral and central tolerance.

3.3. Omenn syndrome (OS)

OS is a severe combined immunodeficiency (SCID) initially described in 1965. It is usually caused by mutations at the level of the recombination-activating (*RAG) 1* or *2* genes. However, mutations in *RMRP*, *ADA*, *ARTEMIS*, and *IL2RG* have also been described. Mutations in *RAG* impair the process of VDJ recombination in both B− and T-cell receptors [29]. It usually manifests in early childhood with the presence of erythroderma, recurrent infections, organomegalies, persistent diarrhea, alopecia, growth retardation, and specific paraclinical findings such as lymphocytosis and elevated IgE levels [91].

Some autoimmune conditions have been associated with OS including HT [92] and IBD [93]. Somech et al. [30] found that T-cell oligoclonal expansion in OS emanates from an incomplete block before the maturation stage of negative selection. This may explain the escape of autoreactive T cells from the thymus and the development of autoimmunity in these patients. Cavadini et al. [94] found that 2 patients with OS showed *AIRE* deficiency in the thymus which may explain the escape of T cells before negative selection. Thereafter, these cells expand on the periphery and cause massive autoimmune reactions. Furthermore, patients with OS exhibited a low population of $FOXP3^{+}$ in the lymph nodes and thymus, and those $CD4^{+}$ $CD25^{+high}$ T cells were unable to suppress the proliferation of autologous or allogenic $CD4^{+}$ responder T cells [95]. These data suggest that patients with OS exhibit defects in central and peripheral tolerance that could be associated with the development of autoimmunity.

3.4. DiGeorge syndrome (DGS)

In 1965, Angelo DiGeorge described postmortem findings in a group of children who lacked thymus and parathyroid glands. However, it not was until 1981 that A. de la Chapelle discovered the chromosomal defect involved in this disease [96]. DGS has an autosomal dominant pattern of inheritance, and it is caused by a deletion in chromosome 22q11 in approximately 95% of patients. This results in disturbances of the central tolerance mechanisms with the resulting escape of autoreactive T cells and an altered production of $CD4^{+}$ $CD25^{+}$ regulatory T cells [97]. The 22q11.2 region contains defined genes such as *TBX1* and is one of the most complex areas of the genome. *TBX1* has been extensively studied in murine models in which the alteration of this gene is associated with cardiovascular, thymic, and parathyroid defects, a phenotype that is similar to the one seen in 22q11 deletion [98]. Recent studies in humans have detected new mutations that could explain the clinical spectrum of the syndrome [99]. The estimated prevalence varies from 1:4000 to 1:6000 without sex or ethnic differences [100].

The presence of a typical facial appearance, congenital heart defects (e.g., interrupted aortic arch, ventricular septal defect, and tetralogy of Fallot as the most common, and pulmonary atresia with interventricular communication and truncus arteriosus as the least common), cleft palate, and early-onset hypocalcemia are considered characteristic of the disease. Other manifestations such as viral and bacterial infections of the upper and lower respiratory tract, delays in speech development, a deficit of working memory that hinders abstract reasoning, behavioral disorders such as attention deficit and anxiety, seizures, and schizophrenia in adult life may be present as well [101,102].

As in other PIDs, DGS is associated with an increased incidence of ADs. A 10% prevalence of ADs in patients with 22q11.2 deletion [103], mainly autoimmune cytopenias, has been reported. Several case reports note the presence of ITP and Evans syndrome (i.e., hemolytic anemia and thrombocytopenia) [104–106]. It is notable that in the case-report of Hernández-Nieto et al. [105], a patient with a partial 22q11 deletion who first presented with autoimmune thrombocytopenia, developed DGS after 2 years of follow-up, presenting with recurrent upper-airway infections and velopharyngeal incompetence. In some cases, autoimmunity may precede the onset of immunodeficiency.

Although DGS is usually diagnosed in early childhood, Nakada et al. [107] reported a 36-year-old adult who presented DGS associated with HT and hypoparathyroidism. Patients with HT may also present with pernicious anemia, atrophic gastritis, idiopathic thrombocytopenic purpura, and psoriasis arthritis [103] thus exhibiting a PolyA phenotype (i.e., more than one AD in the same patient) [108]. Furthermore, pediatric and elderly patients with a 22q11.2 deletion, may also develop GD with anti-thyroid-stimulating hormone receptor antibodies [109,110]. Other ADs such as IBD [111,112], JIA [112–114], and T1D have been associated with DGS [115]. In one study, the prevalence of JIA was higher in patients with 22q11 deletion (3.75%) than in the general population, and the patients exhibited high risk alleles associated with JIA (i.e., HLA-DQ6, HLA-DPB1*0301, HLA-DRB1*0801, HLA-DQB1*0402, HLA-DQ6, DPB1*0301) [113]. These data suggest that other genetic factors besides the 22q11.2 deletion may influence the development of autoimmune phenotypes in DGS.

Although the mechanisms associated with DGS and autoimmunity are not completely elucidated, some studies point to a reduced production of Treg cells. The thymic abnormality is not exclusive to any particular component of T cells, and may affect production of $CD4^+$ $CD25^{+high}$ T cells [27]. As mentioned, dysregulation of these cells has been widely associated with the development of autoimmunity [116]. In the study done by Sullivan et al. [117], patients with DGS exhibited a lower $CD4^+$ $CD25^{+high}$ T count than healthy subjects. This is in line with the hypothesis that patients with thymic aplasia may have reduced levels of Treg cells. Furthermore, as was also mentioned, other genes such as *AIRE* are involved in the negative selection of autoreactive T-cells [27]. Since patients with DGS show impaired function in the thymus, this may result in impaired expression of *AIRE* and defective central tolerance, which ultimately may allow the escape of autoreactive T cells that enable the appearance of ADs [27].

3.5. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)

IPEX was described by Powell et al. in 1982 in a family of 19 subjects [118]. IPEX is an X-linked recessive syndrome that is caused by mutations in the *FOXP3* gene. This gene is involved in the transcription of Treg cells, and it is thought to play a role in the increasing levels of IgA and IgE for B cells, a characteristic feature of IPEX syndrome [119]. To our knowledge, there is no data on the prevalence of this syndrome, since fewer than 300 individuals suffering from the disease have been identified worldwide. Men exhibit milder symptoms, and the disease may present in an older population [120].

This syndrome has an incomplete penetrance and variable expression secondary to epigenetic and environmental factors. Classically, it presents a triad of components including polyendocrinopathy, enteropathy, and eczematous dermatitis [121]. Gastrointestinal symptoms are the most typical manifestations of the disease, typically presenting at about 6 months of age, and often requiring parenteral nutrition. IPEX generally presents with an early onset and progresses with new manifestations over time. Patients may experience fatal outcomes due to sepsis or meningitis mainly caused by *Enterococcus* spp*, Staphylococcus* spp*, Pneumocystis jiroveci,* Candida, and viruses such as cytomegalovirus and Epstein-Barr virus (EBV) [122].

T1D and thyroid disease are the most frequent endocrine manifestations [123]. Hwang et al. [124] documented that *FOXP3* mutations can cause early onset T1D. In some cases, pancreatic destruction can occur in the absence of detectable autoantibodies. Romano et al. [125] reported a case of a neonate who presented with hyperglycemia a few hours after birth with altered plasma levels of insulin and C-peptide that confirmed the presence of neonatal T1D. Other patients may exhibit 24 additional manifestations in conjunction with T1D, including hypothyroidism, haemolytic anaemia, thrombocytopenia, eczema, or atopy [122,126–128].

The mechanisms associated with autoimmunity in IPEX syndrome are not clearly defined. In the study of Chen et al. [129], a high GATA3 expression was found in T cells in the gut and kidneys of patients with IPEX syndrome. These were reduced after immunomodulatory treatment. Furthermore, patients with IPEX showed an increase in Th17 cells associated with high levels of IL-17, IL-6, and IL-23 [40]. In addition, mature naive B cells from IPEX patients exhibited a high expression of autoreactive antibodies in the presence of defective Treg response. These data suggest that Treg cells are the central players in the development of autoimmunity in immunodeficiencies and should be the target of new therapies for these patients.

3.6. Selective (SIgA) deficiency

The selective IgA (*SIgA)* deficiency is the most frequent PID in both children and adults. According to the ESID criteria, it is defined by IgA levels lower than 0.07 g/L, absence of IgG, IgM deficiency, and a typical appearance after the first 4 years of life [130]. IgA is the most abundant isotype and plays a crucial role in the innate and adaptive response. There are different postulates regarding the pathophysiology of the disease: 1) maturation defect in B cells with co-expression of IgM and IgG, 2) T-cell dysfunction, and 3) abnormalities in the cytokine network [131]. The epidemiological data differs depending on the ethnic groups. On the Arabian peninsula 700/100,000 have been reported [132]. Other reports include: 1/173 from a Swedish study in 2009 [133], 1/875 in England [134], 1/223 to 1/1000 in community studies in the USA, and the lowest incidence in Asians (i.e., 1/3230) [135].

The clinical manifestations vary depending on age. Patients can present with recurrent infections and may have a high risk of allergic and ADs [136]. In 1972, Panush et al. [137] found that some patients with JIA and RA showed SIgA deficiency. However, the prevalence of SIgA deficiency in a cohort of 83 patients with JIA was low (1.2%), and it was only high in those patients with partial IgA deficiency (7.1%) [138]. Although the mechanisms associated with these phenomena are unclear, it was recently found that some patients with SIgA deficiency and JIA had a 22q11 deletion, thus suggesting a key role for central tolerance in the development of autoimmunity [139].

A decreased IgA level is often first recognized during testing for celiac disease, since a total IgA is part of the test, along with anti-tissue transglutaminase IgA and deaminated gliadin IgA or IgG. Chow et al. [140] performed a retrospective study of 1815 patients (both adults and children) with CD at the “Celiac Disease Center at Columbia University”. They determined that SIgA deficiency was present in about 2% of the patients, whereas in another study, only 0.75% of the patients with CD were found to exhibit SIgA deficiency.

In a separate study, IgA deficiency was also detected in 3% of 200 infants and adolescents with T1D. Two patients exhibited CD and JIA [141]. In contrast, in a study including 126 subjects with T1D, serum and salivary concentrations of IgA were not different from controls [142]. This suggests that factors other than IgA are related to T1D pathogenesis. In the study done by Liblau et al. [143], the objective was to confirm the hypothesis that HLA-DQB1 alleles encoding non-Asp amino acids at position 57, which are considered a common risk factor for T1D and IgA deficiency, could be the missing link between diseases. However, the presence of HLA-DQB1 alleles was not associated with the incidence of SIgA deficiency. Further studies to identify the common factors between these diseases are warranted.

Other ADs such as Evans syndrome [144], IBD, SS [145], SLE [146],

VIT [147], and AITD [148,149] have been associated with IgA deficiency. Although the mechanisms associated with SIgA deficiency and ADs are not clear, the fact that certain HLA haplotypes confer risk of both SIgA and ADs [150] and that there is a preponderance of familial clustering, points to genetics as a central player in their development [151]. In addition, according to Jacob et al. [152], interactions of monomeric IgA with FcαRI may result in a partial phosphorylation of FcRγ-associated FcαRI, notably in the immunoreceptor tyrosine-based activation motif (ITAM), by inducing the recruitment of the SHP-1 tyrosine phosphatase. This triggers several activating pathways in the immune system including immunoreceptors that bear the ITAM motif and ITAM-independent receptors.

3.7. LRBA deficiency and CTLA-4 deficiency

LRBA deficiency is a genetic disorder of the immune system caused by mutations in the *LRBA*. It was described in 2012 as a new PID with an autosomal recessive inheritance pattern [153]. LRBA deficiency leads to a dysregulation of activated T cells, predominantly Treg cells, defects in the activation of B cells, and the production of immunoglobulins [42]. This disease is characterized by recurrent infections in the upper respiratory tract, hypogammaglobulinemia, and autoimmune manifestations.

The LRBA is closely related to *CTLA-4*, which is located in the cellular membrane of the activated T-cell. The latter regulates peripheral tolerance by inhibiting the activation of T lymphocytes, through negative signaling, competitive inhibition of CD28, or elimination of ligands from antigen-presenting cells [43]. In murine models, CTLA-4 deficiency leads to a lethal phenotype characterized by lymphocytic infiltration [154].

CTLA-4 deficiency is an uncommon disease that presents various manifestations such as adenomegalias, gut disease, and respiratory infections. The different polymorphisms of *CTLA-4* have been considered risk factors for the development of ADs such as HT [155], PBC (polymorphisms in rs231725) [156], and T1D [157]. Lee et al. [158] did a meta-analysis to evaluate the association between the different polymorphisms in *CTLA-4* and their correlation with SLE. The authors found that the polymorphism in exon-1 + 49 GG genotype was predominantly associated with SLE in the Asian population.

LRBA deficiency has also been associated with ADs such as IBD [159], T1D [160], JIA [161], SLE [162], AITD, and polyarthritis [163]. Note that patients with mutations in the *LRBA* gene may initially present with an AD without immunodeficiency [164]. The mechanisms associated with autoimmunity are not clear. However, some studies have shown that Treg cells are the central player in both LRBA and CTLA-4 deficiencies [10]. LRBA was demonstrated to be co-localized with CTLA-4 in endosomal vesicles, and as a result, LRBA deficiency resulted in reduced levels of the CTLA-4 protein in Tregs and activated conventional T cells [165]. These data indicate a close relationship between these two molecules in the pathogenesis of immunodeficiency and autoimmunity.

Patients with LRBA deficiency show impaired function in activated T-cells due to the marked Treg cell depletion and impaired Treg cell-mediated suppression because of the serious deficiency of CTLA-4 expression [165,166]. Furthermore, patients with LRBA mutations showed disturbed B-cell development, defective in-vitro B-cell activation, immunoglobulin secretion, plasmablast formation as well as low proliferative responses which are associated with a high rate of apoptosis, hypogammaglobinemia, and autoimmunity [153]. In addition, patients with IBD, exhibited increased $CD21^{low}$ B cells, which have previously been associated with the autoimmune phenotype [167].

3.8. Common variable immunodeficiency (CVID)

CVID is the second most frequent immunodeficiency worldwide and the most common treatable PID. CVID may have an autosomal recessive or autosomal dominant inheritance (15% of the cases). According to the international consensus document (ICON), it is characterized by low serum levels of IgG (usually < 3 g/L), low serum levels of IgA (< 0.05 g/L) or low IgM, and poor to absent specific antibody production (< 0.3 g/L) [168]. The epidemiological data reported in national registries in different countries show different results. These variations can be explained by access to medical care, diagnostic rates, and genetic and epigenetic factors in different populations. The most common clinical manifestations are the presence of recurrent infections, both bacterial and viral, within short periods of time, partial response to antibiotics, inability to produce antibodies after immunizations, hypogammaglobulinemia unexplained by another cause, autoimmune cytopenias, bronchiectasis, granuloma, malignancies, and ADs [169].

The pathophysiology of this disease has been widely studied. There are four clinically significant primary immune defects: 1) Hypogammaglobulinemia, 2) T-cell activation/proliferation defects, 3) dendritic cell defects, and 4) cytokine deficiencies [168]. Defects in central selection and signaling, activation/proliferation of B cells, and hypogammaglobulinemia are key features of the disease [170]. A relative loss of function and proliferation of T cells has been described in several subjects. This loss leads to a reduction in circulating $CD4^+$ T cells and antigen-specific T cells, and abnormalities in Tregs which can lead to autoimmunity or chronic inflammation [171]. The stimulation of dendritic cells through Toll-like receptors 7, 8, and 9 is down regulated in some patients with CVID, and stimulation is associated with low levels of memory B cells [172]. Defective secretion of regulatory cytokines, including IL-2, IFN-γ, and IL-10 and an increase in the levels of IL-6 and IL-12 (proinflammatory cytokines), may also exist.

ADs are present in about 20% of CVID cases [68]. Tanus et al. [173] reported the first case of polyautoimmunity in CVID in 1993. The patient presented PBC, VIT, atrophic gastritis, and PA. In CVID patients, the most common ADs are cytopenias such as AIHA [174] and ITP [175]. Other ADs such as PA [176], SLE [177], JIA [178], T1D [179], VIT [180], and IBD [181,182] have also been reported. Azizi et al. [183] did a retrospective cohort study that included 227 patients with CVID listed on the Iranian PID Registry. JIA and RA were the most commonly associated ADs.

B-cell is considered the cornerstone of this disease since the cardinal manifestation is hypogammaglobinemia [184]. Although peripheral B cells are normal in number, these cells show abnormal maturation with reduced Ig production [184]. Recently, it has been suggested that a defective class switch [185] and loss of hypermutation in CVID [186] may lead to an inability to exclude autoimmune clones since these characteristics have been associated with the development of autoimmunity. Furthermore, patients with CVID showed high levels of APRIL and BAFF [49] which have been associated with systemic ADs such as RA and SLE [50–53]. These patients show low levels of immunomodulatory cytokines such as IL-2, IL-4, and IL-5 [187] associated with a low expression of FOXP3 in Treg cells [188]. Thus, this complex disease appeared to be associated with defects in central and peripheral tolerance that perpetuate autoimmune phenomena.

3.9. Chronic granulomatous disease (CGD)

Chronic granulomatous disease (CGD) is an infrequent immunodeficiency caused by mutations in a subunit of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. CGD presents with a failure of XLA phagocytosis and predisposes the individual to present infections by catalase-positive germs. According to genetic analysis, when CGD is caused by mutations in the CYBB gene (70% of cases), the disorder is inherited in an X-linked recessive pattern. In contrast, when it is caused by *CYBA, NCF1, NCF2, or NCF4* gene mutations, the condition is inherited in an autosomal recessive pattern [189]. Polymorphisms at the *NCF* gene have been associated with ADs such as SLE, RA, and CD [190–193].

The incidence of CGD is 1:250,000 in the United States [194] and

1:450,000 in Sweden [195]. CGD should be suspected in patients with granulomatous colitis and recurrent bacterial and fungal infections. CGD is characterized by the presence of recurrent pyogenic or fungal skin infections, pneumonia (mainly caused by *Aspergillus* spp., *Klebsiella pneumoniae*, Nocardia), suppurative adenitis, hepatic abscesses (*Staphylococcus aureus*), osteomyelitis, gastrointestinal infections, and growth retardation [196].

Recently, the CGD has been associated with ADs such as SLE [197,198], IBD [199,200], JIA [201], AIT [202], thrombocytopenic purpura [203], RA [193], T1D [204], JIA, and antiphospholipid syndrome [205]. The mechanisms associated with the appearance of ADs in CGD are not clear. However, some studies suggest that Treg cells play a central role in this phenomenon. Deficiency in NADPH oxidase impairs the production of ROS which is considered necessary for macrophages to activate Treg cells [44]. Furthermore, the NADPH oxidase is pivotal in phagosomal proteolysis by dendritic cells (DC) [206] and may regulate antigen presentation by major histocompatibility complex (MHC) class I in DC [207], and MHC class II in B cells [208]. Whether these processes are associated with autoimmunity is still unknown. Further studies to clarify the effect of chronic infection on ADs via molecular mimicry or bystander activation are warranted [21].

3.10. X-linked lymphoproliferative disease (XLP)

X-linked lymphoproliferative (XLP) or Duncan's disease was initially described as a lymphoproliferative syndrome associated with infection by the EBV [209]. The disease is caused by mutations in the gene *SH2D1A*. Its identification has helped in the diagnosis of the disease as well as increased the comprehension of signaling pathways regulated by members of the SLAM family [210]. *SH2D1A* encodes a protein called SAP involved in bidirectional stimulation of T and B cells, production of immunoglobulins, and modification of signaling pathways in T, B, and NK cells [211]. Without the SAP protein, the TCR signal is insufficient for optimal expression of pro-apoptotic molecules such as FasL and BIM [212] which are associated with the lymphoproliferative phenotype. The existence of another mutation located in *XIAP* gene has also been documented [213]. The lack of expression of XIAP is associated with an increase in apoptosis in lymphocytes [210].

The main feature include hemophagocytic lymphohistiocytosis (HLH) which is the most frequent as well as lethal presentation [214]. Other manifestations described include aplastic anemia, vasculitis, chronic gastritis, and cutaneous lesions [211], all of which may be autoimmune related. The mechanisms associated with this phenomenon are not well understood.

3.11. Wiskott-Aldrich syndrome (WAS)

The Wiskott-Aldrich syndrome is an uncommon disease with an inheritance pattern linked to the X chromosome and caused by a mutation in the WASp gene that codes for the WASp protein expressed in the cytoplasm of hematopoietic cells. Its main function is signal transduction to the actin cytoskeleton from the cell surface. Patients with WAS have defects in humoral and cellular immunity. Immunological abnormalities affect the cytoskeleton and T-cell signaling pathways and the production of IFN-γ [215]. In the United States, WAS accounts for 1.2% of the patients with PIDs [216].

The three clinical characteristics of WAS, thrombocytopenia, eczema, and recurrent infections by viruses, bacteria, or encapsulated germs, and appearance early in life [217]. Patients with WAS have a higher risk of developing autoimmune disorders and malignancy. In a French study, Dupuis-Girod et al. [218] evaluated the frequency of autoimmune manifestations in WAS and found that AIHA, detected in 20/55 patients (36%), was the most common autoimmune manifestation. Other ADs included arthritis in 29%, autoimmune neutropenia (AIN) in 25% of the patients, followed by vasculitis in 22%, while SLE and primary sclerosing cholangitis (PSC) were considered less common manifestations [219,220].

IgA nephropathy was described in a case-report on an 8-year-old boy with an insertion at the 1023rd base pair in exon 10 and amino acid substitution (Leu342Thr) [221]. In a retrospective study in Japan between July 2015 and July 2016, a total of 18 patients with a diagnosis of IBD were studied. Mutation of WAS c.1378C > T, p. Pro460Ser was described in three patients [222]. Whether these mutations are associated with ADs in WAS is unknown. However, Bouma et al. [41] developed an experimental model of antigen-induced arthritis in WASp-deficient mice (WAS KO) and documented reduced levels of both Breg and Treg cells associated with an increase in the Th17 population.

3.12. Autoimmune Lymphoproliferative syndrome (ALPS)

The ALPS or Canale-Smith Syndrome is a rare clinical disease that mostly presents an autosomal dominant inheritance pattern and it is characterized by mutations in the *FAS* (70%) followed by mutations in *CASP10* and *FASL* genes. Rathmell and Goodnow described a model that explained the role of FASL/FAS in ALPS. FAS is a surface receptor that binds to FASL and forms a complex that together with caspase-8 and -10 activates the signaling cascade that leads to proteolysis, DNA degradation, and apoptosis [223]. Mutations at the level of these receptors give rise to defective apoptosis of the lymphocyte that causes an alteration in the immune homeostasis thus producing an accumulation of auto reactive lymphocytes in secondary lymphoid organs [55,56].

Genetic advances and genome sequencing have revealed new candidate genes that include *KRAS, NRAS, CTLA4, LRBA, MAGT1, STAT3*, and *TNFAIP3* [224]. Initially, ALPS was classified into seven different groups based on the genetic defect. However, they have now been reassigned into 3 possible categories: ALPS-FAS, ALPS-Sfas, and ALPS-FASLG. The prevalence of ALPS is unknown due to difficulties in early diagnosis. It affects men and women equally and includes different ethnic groups [225].

The clinical presentation of ALPS is variable and involves a variety of hematologic abnormalities. Lymphoproliferative disorders are the most common clinical presentation and may include lymphadenopathy, mild to moderate hepatomegaly, or generally moderate splenomegaly that persists throughout life [18]. Autoimmunity is the second most common clinical manifestation, primarily characterized by cytopenias (i.e., AIHA, ITP and AIN) [18,226,227]. Patients with ALPS and other family members have a high risk of developing malignancy, mostly B-cell lymphomas [225].

FAS plays an indispensable role in the proliferation of lymphocytes, and peripheral tolerance is involved in not only the defense of the individual but also the prevention of autoimmune manifestations. Mutations in the receptors involved in the pathway of apoptosis cause alterations in immune homeostasis leading to an accumulation of autoreactive lymphocytes which condition the patient to the development of autoimmunity [18]. This is considered the most likely mechanism for autoimmunity in ALPS patients.

3.13. Complement deficiencies

The complement cascade is a fundamental component of the innate immune system. The main functions of complement are opsonization and disruption of the integrity of membranes. The C1q component affects not only the activation of the complement through the classical route but also the elimination of apoptotic cells, C3 and C4 opsonization activity, and chemotaxis [60]. Deficiencies in components of the complement system are classically associated with infections like pneumococcal or meningococcal sepsis, meningitis, and arthritis. However, there are other non-infectious manifestations such as cutaneous hereditary angioedema (HAE), and SLE which are partially explained by a defective elimination of immune complexes and apoptotic cells. SLE is identified in 93% of the patients with C1q component deficiency, with a somewhat lower association with C4 and C2 deficiency

[61–63].

Several authors have studied the coexistence of SLE in patients with complement deficiencies. Aggarwal et al. [228] did a study on a large cohort of 544 members of familial SLE and determined that SLE was more commonly established in families with hereditary complement deficiency. Gilliam et al. [229] studied 61 patients with JIA, SLE, RA, and mixed connective tissue disease. They found that 5/35 patients from the JIA group had partial C4 deficiency. In addition, one case of dermatomyositis (DM) was reported in a 60 year old patient with hereditary C2 deficiency and a 37 autosomal recessive pattern of inheritance [230]. The deficiency of components of the complement pathway contributes to inflammatory processes and increases the risk of ADs, mainly SLE [231].

3.14. Hyper- IgM syndrome (HIGM)

The Hyper-IgM syndrome is characterized by alterations of a specific isotype of the immunoglobulin receptor and normal or elevated levels of IgM associated with low levels of IgA, IgG, and IgE. The most frequent type is X-linked (65–70%) and has a variable presentation. Of the seven different mutations associated with HIGM, those affecting the gene encoding for CD40L represents most cases. An increase in reactive B cells with decreased $CD3^+$ $FOXP3^+$ cells has been reported and suggests defects in the mechanism of peripheral tolerance as well as an imbalance in cytokine production [48]. The most common clinical manifestations are infections of the respiratory tract caused by bacteria, viruses such as cytomegalovirus, fungi such as cryptococcal, and gastrointestinal alterations with or without malabsorption.

Levy *el al.* [232] evaluated 56 patients with HIGM1 with CD40L gene mutation or defective CD40L expression, and found that 6% had IBD, 11% had arthritis, 19.6% had PSC, and 67.8% had neutropenia. Webster et al. [233] found that 17.7% of the patients with HIGM presented arthritis as the initial manifestation. Sibilia et al. [234] reported a case of Hyper-IgM Syndrome diagnosed in a 12-year-old child who at the age of 42 developed RA, and Qiu et al. [235] described the first report of hemizygous CD40LGc.542G > mutation in a patient with Crohn's disease. Although the mechanisms for autoimmunity are not clear, dysfunction in the interaction of CD40-CD40L, which is involved in the selection of Treg cells, appears to play a key role in the development of autoimmune phenomena. Impairment in CD40-CD40L signaling leads to an increase in circulating reactive T cells [48]. In addition, patients with CD40 deficiency present with an imbalance in cytokines involved in the maturation of dendritic cells [64].

3.15. Hyper-IgE syndrome (HIES)

The Hyper-IgE syndrome or Job Syndrome was described in 1966. It is considered a rare disorder, and it has been documented as having an autosomal dominant and recessive form. The latter has a greater predisposition to viral skin infection and severe eczema [236]. It is caused by different mutations, one of which is in the tyrosine kinase 2 (*TYK2*) gene involved in the JAK-STAT signaling pathway (signal transducer and transcription activator) [237]. Another mutation is in *DOCK8* gene characterized by severe viral skin infections together with an increased risk of malignancy [238]. Others are heterozygous mutations in STAT 3 with IL-6 and IL-10 deficiency and the failure of differentiation of Th17 cells leading to a higher incidence of pneumonia and pneumatoceles [239,240].

Clinical manifestations include recurrent staphylococcal cutaneous abscesses, pneumonia with pneumococcal formation, eczema, dental anomalies and elevated levels of serum IgE. These patients also have autoimmune manifestations such as RA, ITP [241], SLE [242,243], and bullous pemphigoid [244]. In some cases, ADs precede the appearance of Hyper-IgE syndrome. Saikia et al. [245] described a case of a child who developed juvenile dermatomyositis (JDM) at the age of 3.5 years and 8 years later presented Hyper-IgE syndrome. Some data suggest that patients with HIES exhibit defects in the transduction of signals with an alteration of cytokines. This leads to impaired Th17 function which results in the development of immunological manifestations including autoimmunity [246]. However, given the low prevalence of this syndrome, the mechanisms relaying this disease are not well understood.

3.16. Ataxia telangiectasia (A-T)

A-T is an unusual PID in childhood characterized by a mutation in the *ATM* that codes for the ATM protein serine/threonine kinase involved in the regulation of cell division, repair, and genome stability. The most common presentation includes low levels of immunoglobulins or moderate lymphopenia associated with a decrease in the number of absolute and naïve $CD4^+$ T cells [247]. The incidence of A-T in the USA is close to 1 in 100,000 live births, equally distributed between the sexes [248].

Clinical manifestations include ataxia, recurrent sinopulmonary infections, and vasculitis. There is a high risk of malignancy, especially non-Hodgkin lymphomas, lymphocytic leukemias, and solid tumors. These patients have a higher frequency of autoimmune disorders such as HT. Patiroglu et al. [249] reported a case of a patient diagnosed at 4 years of age with A-T and later development of HT. Pasini et al. [250] reported the case of a child with A-T who developed JIA 14 years after the onset of the disease. Other common autoimmune conditions include ITP [251] and AIHA [252]. Although the mechanisms in autoimmunity are not clear, a mutation in the ATM gene causes uncontrolled growth and division in cells with alterations at the level of protein production [253].

3.17. STAT deficiency

The JAK-STAT signaling pathway is commonly involved in both ADs and PIDs [254]. STAT proteins are a family of transcription factors composed of seven members. STAT1, STAT3, and STAT5B play an important role in the development of autoimmunity [255]. Mutations at the STAT1 level produce an increase in the signaling pathway of IFN-γ and inhibition of IL-17 secretion [256]. Characteristically, STAT deficiency presents with CMC, recurrent infections by bacteria, herpes virus, disseminated coccidiodomycosis, and histoplasmosis [257]. Partial STAT1 deficiency is related to susceptibility to mycobacteria, whereas complete STAT1 deficiency is frequently associated with viral and disseminated mycobacterial infections [20]. Thyroiditis with elevated thyroid antibodies is the most frequent autoimmune manifestation and has a high prevalence in patients with mutated STAT1 [258]. Other ADs such as AIHA, ITP, and CD have also been reported [258,259].

A mutation in STAT3 leads to a reduction in the TH17 cell count and a resulting alteration in the production of IL-17. Other effects include a deficiency in NK and dendritic cells, as well as an interruption in the maturation of B cells [260]. The mutation in STAT3 leads to early autoimmune manifestations such as the neonatal T1D described by Velayos et al. [261]. Other manifestations include interstitial pneumonitis, and RA in which STAT3 is considered a crucial mediator in the development of chronic inflammation as a result of the increased expression of inflammatory cytokines such as IL-6, IL-1, and TNF-α [262].

STAT5B mutations cause alterations in the Treg cells with a simultaneous decrease in γδ and NK cell populations [45]. Patients with this mutation exhibit growth retardation, chronic lung disease, allergies, and autoimmune manifestations including JIA, ITP, and AITD. The first case of STAT5B deficiency was reported in 2003. It was caused by a missense mutation (p.A630P), and the patient presented with growth retardation, lymphocytic interstitial pneumonitis, and a severe varicella zoster infection [263]. Pulmonary pathology is the most common expression in these patients and studies have established an association between deficiency of STAT5B and immune dysfunction mediated by Treg cells [45].

3.18. ORAI1 and STIM1 deficiency

Intracellular calcium acts as a second messenger in the regulation of expression and gene transcription, cellular differentiation, and the secretion of cytokines. The CRAC channels consist of two essential proteins known as STIM1 and ORAI1 that are essential to distinguishing FcγR-induced signaling events in macrophages [264]. ORAI1 is predominantly expressed in primary and secondary lymphoid organs but is found in almost any organ in the body, whereas STIM 1 is mostly expressed in lymphocytes, skeletal and cardiac muscle, the brain, and pancreas.

The expression of defective proteins in mutant ORAI1 R91W, A88EfsX25, A103E, and L194P generates an alteration in the activation of T cells and in the production of cytokines as well as a defect in the fast-twitch muscle fiber [265]. Patients with STIM1 deficiency have a phenotype similar to the one found in ORAI1 deficiency. Mutations at E136× and 1538-1G > A in *STIM1* lead to impaired function and proliferation of T cells and reduced cytokine secretion [266]. The prevalence of the disease is unknown and data about sex predisposition is lacking.

Mutations of these two genes (i.e., *ORAI1 and STIM1)* cause recurrent infections, autoimmune conditions, ectodermal dysplasia, and congenital myopathy [267,268]. T cells, B cells, and NK cells are numerically intact. The defect is in T cell activation, not in lymphocyte development. Whereas reduced levels of Treg cells provide an explanation for the characteristic symptoms of the disease, usually beginning in the first year of life, factors such as negative selection of autoreactive T cells contribute to autoimmune manifestations such as AIHA and ITP [268].

3.19. CD25 deficiency

The CD25 plays an indispensable role as a component of the high affinity IL-2 receptor and in the normal functioning of the Treg cells [269]. Mutations in the IL2 receptor alpha gene (i.e., *IL2RA*) result in an increased susceptibility to infections, and manifestations of lymphoproliferation such as lymphadenopathy and hepatosplenomegaly. These patients showed defective IL-10 expression from $CD4^+$ T-cells generating manifestations similar to the IPEX syndrome [39].

CD25 deficiency has been associated with ADs including T1D, bullous pemphigoid, autoimmune cytopenias, and AITD [37]. Goudy et al. [37] reported an 8-year-old girl who developed enteropathy associated with eczema during her first month of life, then developed bullous pemphigoid in her first year, and at the age of 4, was diagnosed with autoimmune thyroiditis. Since CD25 is required for the functioning of Treg cells, it is tempting to speculate that a malfunction of these receptors on Tregs may explain the appearance of ADs in patients with this PID.

4. Laboratory assessment

Patients with PIDs present a varied expression of disease from mild manifestations to potentially fatal outcomes. Thus, an early diagnosis based on clinical suspicion and laboratory data that support the therapeutic approach is essential [270]. The clinician should consider the 11 warning signs proposed above (Fig. 3), and laboratory testing may eventually include genetic testing to identify abnormalities in known PID genes such as *BTK, AIRE, FOXP3, RAG1, RAG2, LRBA, CTLA-4, TACI, BAFF-R, WAS, FAS, FASL, CASP8, CASP10, KRAS, NRAS, ATM,*

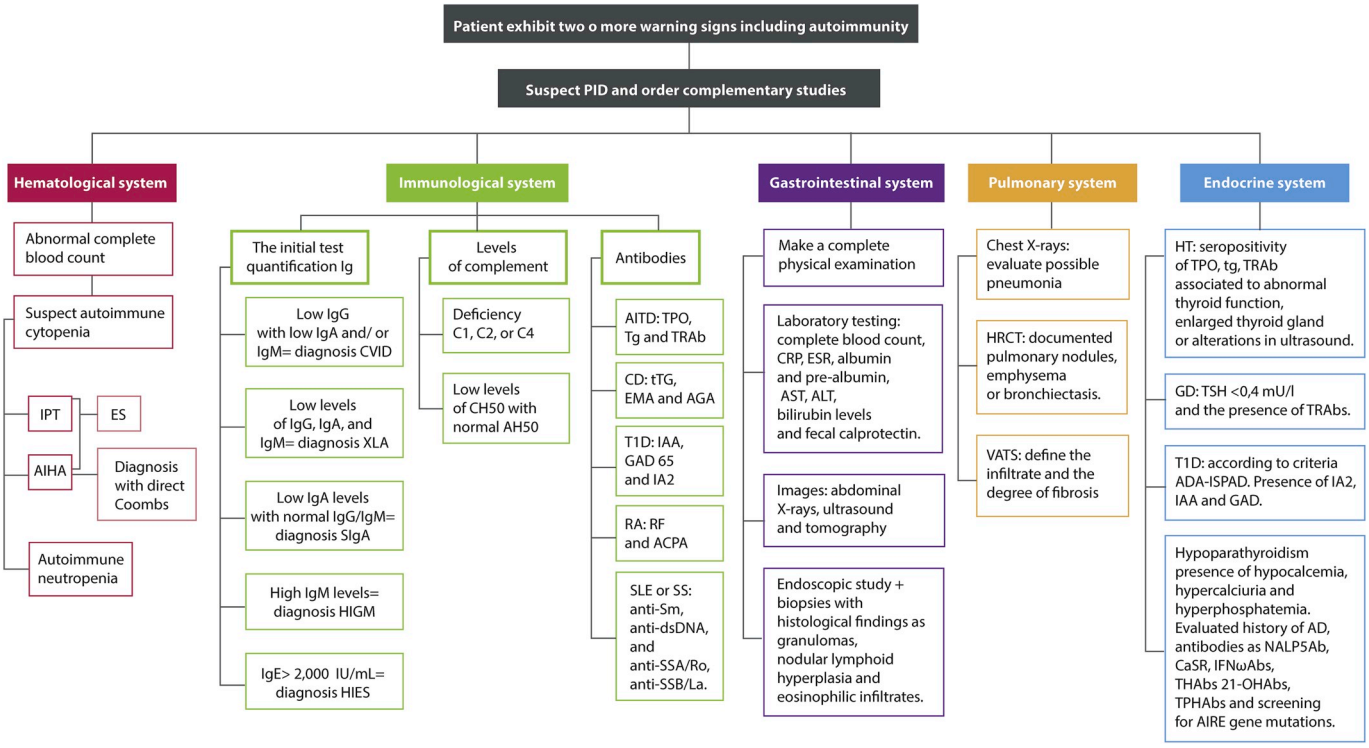

Fig. 4. Rational approach to diagnosis of PIDs and ADs. ACPA: *Anti*-citrullinated protein antibodies; ADs: autoimmune diseases; AGA: anti-gliadin antibodies: AIHA: Autoimmune hemolytic anemia; *AIRE:* autoimmune regulator; AITD: Autoimmune thyroid disease; ALT: Alanine aminotransferase; AST: Aspartate transaminase; CaSR: Calcium-Sensing Receptor; CVID: Common variable immunodeficiency; CRP: C-reactive protein; EMA: endomysial antibody assay; ES: Evan's syndrome; ESR: Erythrosedimentation rate; GAD65: glutamic acid decarboxylase antibodies; GD: Graves' disease; HIES: Hyper-IgE syndrome; HIGM: Hyper-IgM syndrome HRCT: High-resolution computed tomography; HT: Hashimoto thyroiditis; IAA: Insulin autoantibodies; IA2: Protein tyrosine phosphatase antibodies; IFNωAbs: interferon-omega autoantibodies; ITP: Immune thrombocytopenic purpura; NALP5Ab: NACHT leucine-rich-repeat protein 5 autoantibodies; PIDs: primary immunodeficiencies; RF: Rheumatoid factor; SIgAD: selective immunoglobulin IgA deficiency; SLE: Systemic lupus erythematosus; SS: Sjogren's syndrome; THAbs: tyrosine hydroxylase autoantibodies; TPHAbs: tryptophan hydroxylase autoantibodies; TPO: *Anti*-thyroperoxidase antibodies; TRAb: Thyroid-stimulating hormone receptor; tTG: tissue Transglutaminase antibody 21-OHAbs: 21- hydroxylase autoantibodies.

STAT1, STAT3, STAT5B, ORAI, and *STIM1*. A wide range of genetic panels for PID are now available. But before that, non-genetic testing can also help identify clues that will help direct the clinician to the appropriate genetic tests that will help make the diagnosis of PID and AD (Fig. 4).

4.1. Hematological system

As previously discussed, ITP is the most frequent hematological manifestation followed by AIHA, and some patients show both conditions simultaneously (i.e., Evans syndrome) [271]. In patients with persistent bicytopenia or pancytopenia with no indication of autoimmunity, a bone marrow biopsy should be done in order to rule out or confirm malignancy or bone marrow failure syndrome [272].

4.2. Immunological system

Deficiencies in the production of antibodies is commonly observed in the majority of patients with PIDs. The initial test is the quantification of immunoglobulins which show different patterns depending on each disease. When hypogammaglobulinemia (i.e., values lower than two SD adjusted for age) or agammaglobulinemia (i.e., IgG values below 100 mg/dL) are detected, an extended immunological study should be done based on the most common Ig patterns in the different PIDs.

CVID requires low IgG with a low IgA and/or IgM and normal B-cell numbers [273]. XLA presents low levels of IgG, IgA, and IgM and very low or absent circulating B cells with normal T-cell quantities [274]. The selective IgA deficiency is characterized by low IgA levels with normal IgG and IgM levels [275]. In the HIGM, there are high IgM levels while in HIES there is an IgE level > 2000 IU/mL with low Th17 cell numbers. OS and IPEX also exhibit high levels of IgE [276].

Considering the role of autoimmune manifestations in patients with PIDs, the measurement of an initial set of autoantibodies covering the most common ADs in those patients is recommended (Tables 1 and 2). These include: 1) IgG *anti*-thyroperoxidase (TPO), IgG anti-thyroglobulin (Tg), IgG, and IgG thyroid-stimulating hormone receptor antibodies (TRAbs) for patients suspected of thyroid autoimmunity; 2) IgA tissue transglutaminase antibodies, endomysial, and anti-gliadin antibodies for patients with gastrointestinal manifestations; 3) insulin autoantibodies (IAA), glutamic acid decarboxylase 65 (GAD65), and protein tyrosine phosphatase (i.e., IA2 or ICA512) antibodies for patients in whom T1D is suspected; 4) RF and IgG *anti*-citrullinated protein antibodies (ACPA) for patients with arthritis; and 5) *anti*-Sm, *anti*-dsDNA, and *anti*-SSA/Ro, and *anti*-SSB/La antibodies for those in whom SLE or SS are suspected respectively. For complement deficiencies, patients with C1, C2, or C4 deficiency present with low levels of classical complement (CH50) function and normal AH50 [270]. A finding of hypocomplementemia should encourage a search for SLE.

4.3. Gastrointestinal system

Gastrointestinal manifestations are frequent in patients with PIDs, especially IPEX, OS, CVID, and CGD. However, given the similarity in clinical presentation, early recognition may be difficult. That is why the diagnosis must have a comprehensive approach that includes a complete physical examination, laboratory studies such as complete blood count, acute phase reactants (CRP and ESR), albumin, pre-albumin, and liver function tests such as AST/ALT and bilirubin levels. Fecal calprotectin is a marker of bowel inflammation that can rise as much as 40 times the normal values during inflammatory processes [277]. For those patients in whom IBD is suspected, a colonoscopy and biopsies should be done. This procedure may provide common histological findings such granulomas, atrophy of the villi of the small intestine, nodular lymphoid hyperplasia, and lymphocytic and eosinophilic infiltrates [278] which could help to the diagnosis of autoimmunity.

4.4. Pulmonary system

Lymphocytic interstitial pneumonitis (LIP) occurs more frequently in patients with CTLA4 deficiency while granulomatous-lymphocytic interstitial lung disease (GLILD) occurs in patients with CVID or LRBA deficiency [279]. As in all conditions, a complete history and physical examination are indispensable for diagnosis along with radiological images such as chest X-rays and high-resolution computed tomography (HRCT) in order to identify pulmonary nodules, emphysema, bronchiectasis, or ground glass opacities [278].

In addition, a video-assisted thoracoscopic (VATS) biopsy is often useful for defining the infiltrate and the degree of fibrosis in some subsets of patients with a poor response to treatment [280]. if the lesions are not accessible, open lung biopsy may be necessary. The recurrent or persistent appearance of pulmonary manifestations may alert physicians to the presence of granulomatous diseases in PID.

4.5. Endocrine system

AITD is the most common AD in the general population and is also frequently found in PIDs such as CVID and IPEX [281]. The diagnosis of HT is based on the seropositivity of *anti*-TPO, *anti*-Tg, *anti*-TSH IgG associated with at least one of the following findings: abnormal thyroid function, enlarged thyroid gland, or abnormal ultrasound findings of thyroid morphology [282], The diagnosis of GD is confirmed by TSH levels at undetectable values (< 0,3 mU/l), high serum free T4 and T3 levels, and the presence of TRAbs [283].

T1D is common in some PIDs such as IPEX syndrome, CVID, and APECED. Clinicians should follow the ADA-ISPAD criteria: “Fasting plasma glucose (minimum 8 h) ≥126 mg/dL (7.0 mmol/L) or 2 h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT) (75-g) or A1C ≥ 6.5%, or random plasma glucose ≥200 mg/dL (11.1 mmol/L)” [284]. The presence of autoantibodies against GAD65, IAA, IA2 and ICA512 may be present but do not necessary diagnose T1D [285].

Abnormal parathyroid function leads to characteristic symptoms of DGS and APECED. Hypoparathyroidism is characterized by the presence of hypocalcemia, hypercalciuria, and hyperphosphatemia [286]. In patients with low PTH levels, a more comprehensive evaluation is required to establish the cause. Testing for antibodies directed against NALP5 (NACHT leucine-rich-repeat protein 5), CaSR (Calcium-Sensing Receptor), and at least one of the following: IFNω (interferon-omega), TH (tyrosine hydroxylase), 21-OH (21- hydroxylase), TPH (tryptophan hydroxylase), or AADC (aromatic L-amino acid decarboxylase), together with screening for *AIRE* gene mutations is recommended [287].

5. Management of autoimmunity in primary immunodeficiency

The fundamental pillars of the treatment of PID are intravenous gamma globulin infusions (IVIg) and antibiotic therapies. At the same time, treatment for the associated ADs will depend on the organic manifestations of these diseases and the pathophysiology underlying these conditions [169]. Management strategies should address not only the spectrum of autoimmunity but also the genetic and/or molecular mechanisms that lead to an alteration in the immune system (Table 3) [169].

Steroids are still accepted as the first line therapy for autoimmune cytopenias, but other newer drugs are becoming increasingly more available. Steroids may be initially used at relatively high doses until cell counts stabilize and then maintained at low doses for a period of 6–12 months. This provides a response rate of around 80% [278]. IVIg are used mainly for patients with AIHA, and other strategies such as inhibitors of complement fixation (i.e, Ecalizumab), cell growth inhibitors (i.e Azathioprine (AZA), Cyclosporine, Mycophenolate Mofetil (MMF), Cyclophosphamide), and cell depleting monoclonal antibodies (i.e, Rituximab, Alemtuzumab) could be used for these patients as

Table 3
Treatment of autoimmunity in patients with primary immunodeficiency.

Category	Autoimmunity	Treatments of choice
Autoimmune hematologic syndromes	ITP, AIHA, ES, AIN	Steroids, immunosuppression (AZA, Vcr, Vbl, CY, MTX, MMF, sirolimus), immunoglobulin G replacement therapy, Rituximab, ATG, Alemtuzumab, HSCT, splenectomy, and bone marrow transplant.
Autoimmune gastrointestinal manifestations	IBD, CD, AIE and PA.	Systemic steroids, NSAIDs, antibiotics, Immunosuppression (6-MP, AZA, cyclosporine), infliximab, adalimumab, etanercept, Vedolizumab, microbiota.
Rheumatic disease	RA, JIA, SLE, SS, DM, SSc, scleroderma.	Hydroxychloroquine, CY, AZA, MMF, DMARDs, Etanercept, Adalimumab, Infliximab, Abatacept, Rituximab, Belimumab
Autoimmune Lung Disease	GLILD	Steroids, Immunosuppression (AZA, CY), Infliximab, Rituximab.
Autoimmune skin disorders	PSO, VIT, eczema, alopecia and pemphigus.	Moisturizing lotions, Steroid ointments, Rituximab.Tofacitinib.

Table taken and modified from Azizi G et al. [169]. Abbreviations: AIE: Autoimmune Enteropathy; AIHA: autoimmune hemolytic anemia AIN: Autoimmune neutropenia; ATG: antithymocyte globulin; AZA: azathioprine CD: celiac disease; CY: cyclophosphamide; DMARDs: disease-modifying antirheumatic drugs; DM: dermatomyositis; GLILD: granulomatous-lymphocytic interstitial lung; HSTC: hematopoietic stem cell transplantation; MMF: mycophenolate mofetil; mTOR: mammalian target of rapamycin; MTX: methotrexate; NSAIDs: nonsteroidal anti-inflammatory drugs; PA: pernicious anemia; PSO: psoriasis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SS: Sjögren's syndrome; VIT: vitiligo; Vcr: vincristine; Vbl: vinblastine.

second line options [272,288]. Rituximab is considered an effective option for managing persistent or chronic autoimmune cytopenias [289]. In the case of patients with WAS and APLS, the second line of treatment is splenectomy with response rates ranging between 20 and 65% [290]. In addition, for patients with APLS associated with autoimmune cytopenias, the first line is corticosteroids and the second line is the MMF. Sirolimus has also been used to produce a sustained remission in patients with refractory autoimmune cytopenias [291]. Thus, treatment of this autoimmune manifestation will depend on the clinical subphenotype as well as the history of clinical response to conventional therapies.

Numerous individuals affected by PID require life-long therapies including IVIg. The individualization of the treatment helps preserve the function of target organs, improves of quality of life and prevents fatal outcomes [292]. IgG replacement therapy is generally indicated for patients with hypogammaglobulinemia. It can be given subcutaneously or intravenously each one to four weeks, depending on the route and the dose. Both routes have been confirmed to be effective but the intravenous one is the most commonly used, although subcutaneous administration is often better tolerated [292].

Patients under routine care with pulmonary compromise secondary to ADs should be treated with immunosuppressants (i.e., AZA or Cyclophosphamide) while those with associated infectious processes should be treated with antimicrobials [169]. If neoplasia is suspected, an oncological assessment should be done [293]. Patients with follicular bronchiolitis have been successfully treated with cell depleting monoclonal antibody (i.e., Rituximab) and T-cell inhibitors (i.e, AZA,MMF) [294].

In patients with CVID or CGD associated with inflammatory bowel disorders, steroids may be enough for treatment. However, in patients where enteropathy is severe, as in OS or IPEX, aggressive immunosuppression may be required, including Cyclosporine or FK506 [295]. Recent studies have shown the effectiveness of Sirolimus in reducing manifestations such as chronic diarrhea. Severe enteropathy refractory to TNF-α inhibitors associated with LRBA deficiency has also been successfully treated with Sirolimus [296].

Biological therapies have been increasingly utilized to treat rheumatological conditions in patients with PIDs. For example, studies have reported the efficacy of rituximab in patients with SLE associated with CVID [297], and the use of Abatacept as a pharmacological therapy is recognized for RA and JIA. Lévy et al. [163] document the case of two siblings with polyautoimmunity associated with LRBA deficiency that was managed with Abatacept with a satisfactory clinical response. T-follicular helper cell frequencies and other markers of immune dysregulation (i.e., soluble CD25, CD45RO + $CD4^+$ effector T cells, and autoantibodies) were found to decrease sharply with CTLA4-Ig therapy and this was predictive of favorable clinical responses in patients with CTLA4 or LRBA deficiency [166]. Although Belimumab is approved by the FDA for treatment of adult patients with SLE, it has not yet been used on patients with CVID, and should be used with caution in patients with BAFF receptor deficiencies [298].

At present, hematopoietic stem cell transplantation (HSCT) is often a consideration in the management of patients with certain PIDs, and it is the treatment of choice for patients with HLH and XLP [299]. Up to 90% cure rates in combined immunodeficiency have been documented, and around 95% in Wiskott-Aldrich syndrome [300]. Recently, it has also been listed as first line therapy in CGD [301]. In 2014, Güngör et al. [302] reported the greatest experience of HSCT in patients with CGD. They described 56 patients who received stem cell transplants between 2003 and 2012 and had survival rates of 93% with a low risk of complications. Yanir et al. [303], showed a higher rate of ADs, such as autoimmune cytopenias and AITD, in 12 of 24 patients following treatment with HSCT. Nevertheless, when appropriate, HSCT is considered a safe treatment that provides for improved symptom control, minimal long-term side effects, and a beneficial impact on quality of life in patients with PID and AD [303].

6. Conclusions

ADs are common in patients with PIDs and can be the first manifestation. Treg cells appeared to be the main factor associated with the appearance of ADs in the majority of patients and are a target for research and therapy. In addition, diagnostic and therapeutic approaches should consider the commonalities between autoimmunity and PIDs. Every child with immunodeficiency should be tested for ADs and vice versa.

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Appendix A. Supplementary data

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