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Review article

Primary immunodeficiency association with systemic lupus erythematosus: review of literature and lessons learned by the Rheumatology Division of a tertiary university hospital at São Paulo, Brazil

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A B S T R A C T

Primary immunodeficiency disorders (PID) represent a heterogeneous group of diseases resulting from inherited defects in the development, maturation and normal function of immune cells; thus, turning individuals susceptible to recurrent infections, allergy, autoimmunity, and malignancies. In this retrospective study, autoimmune diseases (AIDs), in special systemic lupus erythematosus (SLE) which arose associated to the course of PID, are described. Classically, the literature describes three groups of PID associated with SLE: (1) deficiency of Complement pathway components, (2) defects in immunoglobulin synthesis, and (3) chronic granulomatous disease (CGD). Currently, other PID have been described with clinical manifestation of SLE, such as Wiskott–Aldrich syndrome (WAS), autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), autoimmune lymphoproliferative syndrome (ALPS) and idiopathic CD4^{+} lymphocytopenia. Also we present findings from an adult cohort from the outpatient clinic of the Rheumatology Division of Universidade Federal de São Paulo. The PID manifestations found by our study group were considered mild in terms of severity of infections and mortality in early life. Thus, it is possible that some immunodeficiency states are compatible with survival regarding infectious susceptibility; however these states might represent a strong predisposing factor for the development of immune disorders like those observed in SLE.

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Associação de imunodeficiência primária com lúpus eritematoso sistêmico: revisão da literatura e as lições aprendidas pela Divisão de Reumatologia de um hospital universitário terciário em São Paulo

Palavras-chave:
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Deficiência de anticorpos

RESUMO

As imunodeficiências primárias (IDP) representam um grupo heterogêneo de doenças resultantes de defeitos hereditários no desenvolvimento, maturação e função normal de células do sistema imunológico; assim, tornam os indivíduos suscetíveis a infecções recorrentes, alergia, autoimunidade e doenças malignas. Neste estudo retrospectivo, descrevem-se doenças autoimunes (DAI), em especial o lúpus eritematoso sistêmico (LES), que surgiram associadas ao curso das IDP. Classicamente, a literatura descreve três grupos de IDP associadas ao LES: (1) deficiência de componentes da via do complemento, (2) defeitos na síntese de imunoglobulinas e (3) doença granulomatosa crônica (DGC). Na atualidade, outras IDP têm sido descritas como manifestações clínicas do LES, como a síndrome de Wiskott–Aldrich (WAS), a poliendocrinopatia autoimune-candidíase-distrofia ectodérmica (APECED), a síndrome linfoproliferativa autoimune (ALPS) e a linfocitopenia idiopática CD4⁺. Também são apresentados achados de uma coorte de adultos do ambulatório da Divisão de Reumatologia da Universidade Federal de São Paulo. As manifestações de IDP encontradas pelo nosso grupo de estudo foram consideradas leves em termos de gravidade de infecções e mortalidade no início da vida. Assim, é possível que alguns estados de imunodeficiência sejam compatíveis com a sobrevivência em relação à suscetibilidade infecciosa; no entanto, estes estados podem representar um fator de predisposição forte para o desenvolvimento de doenças imunológicas, como observado no LES.

Introduction

Primary immunodeficiency disorders (PID) represent a heterogeneous group of diseases resulting from inherited defects in the development, maturation and normal function of immune cells. PID often have an important genetic basis leading to different immune disorders associated with infections, autoimmune diseases and other malignancies in patients.[1] Since these are congenital conditions, usually with well-defined genetic defects and mendelian inheritance, children are the most predominant patients. On the other hand, autoimmune diseases (AIDs) have a complex multifactorial polygenic etiology in which environmental triggers play an important role in their pathogenesis and represent a group of more than 70 known diseases.[2] Remarkably, AIDs represent one of the most common clinical phenotypes of many forms of PID, only overcome by the frequency of infections.[3]

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease characterized by a range of clinical manifestations that predominantly affects women in reproductive age. In SLE, polyclonal hypergammaglobulinemia and multiple autoantibodies are produced predominantly against nuclear antigens. These autoantibodies deposit on several organs, including kidneys, skin and joints, causing severe inflammation.[4] Although SLE patients have hypergammaglobulinemia, they often present severe infections, especially while receiving immunosuppressive treatment.

Infections by opportunistic pathogens are commonly seen in patients with PID.[5] These infections, either clinical or subclinical, may represent the primary trigger for the development of autoimmunity. In genetically predisposed individuals, chronic exposure to environmental factors can promote the development of autoantibodies many years before the disease onset. Patients with SLE present an increased susceptibility to infection in pre-clinical phase of disease.[6] Classically, the literature describes three groups of PID associated with SLE: (1) deficiency of Complement pathway components[7]; (2) selective and partial defects in immunoglobulin synthesis (particularly isolated IgA and IgM deficiencies)[8,9]; and (3) chronic granulomatous disease (CGD).[9–12] However, among clinical observations, several other PID may also occasionally be associated with SLE or SLE-like syndrome manifestations. These include Wiskott–Aldrich syndrome (WAS),[13] autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED),[14] autoimmune lymphoproliferative syndrome (ALPS),[15] idiopathic CD4⁺ lymphocytopenia (ICL),[16] partial T cell immunodeficiency and hyper-immune dysregulation (including autoimmunity, inflammatory diseases and elevated IgE production).[17]

Our group has reported that a broad fraction of juvenile SLE patients present one of the several forms of PID.[18] More recently, we documented that 28% of a consecutive cohort of 300 adult SLE patients present some form of PID, mainly related to immunoglobulin deficiency. In this review, we describe the various PID associations with SLE or SLE-like manifestations and also our experience from the outpatient clinic of the adult Rheumatology Division at Universidade Federal de São Paulo.

Classical and non-classical PID associated with SLE

PID are a heterogeneous group of diseases characterized by increased susceptibility to multiple and recurrent infections caused by virulent and non-virulent microorganisms. The literature ranks PID in classical and non-classical forms. Classical PID are defined on the basis of an overt immunologic phenotype, often leading to the identification of the disease-causing gene. The expert committee on Primary Immunodeficiency of the International Union of Immunological Societies (IUIS) recently updated the classification of human classical PID.[19] Non-classical PID are defined on the basis of a specific though unremarkable clinical phenotype, and never have been classified as a fully distinct phenotype out of PID classification. Additionally, they have not been included in the updated classification of PID, compiled by the ad hoc Expert Committee of the IUIS.[20] However, the fact that non-classical PID may not be associated with recurrent infections does not guarantee that these diseases do not predispose the development of autoimmune disorders. Therefore, in this paper, we describe the major classical and non-classical PID associated to SLE.

Complement deficiencies

The Complement system is composed by a group of plasma and surface cell-proteins with important role in innate and acquired humoral immune system, responsible for the destruction of microbial agents and clearance of circulating immune complexes.[21] In SLE, the deposition of immune complexes containing multiple autoantibodies and activation of the Complement system mediate tissue damage.[4] Paradoxically, deficiencies in components of early elements of the classical pathway (C1q, C1r, C1s, C4, and C2) are strongly associated with the development of SLE. In addition, deficiency in components of the late common pathway (C5, C6, C7, C8a and C8b) as well as some elements of the alternative pathway (C3 and Factor I) are only occasionally associated with SLE (Table 1).[19] Genetic deficiencies of these components might contribute towards SLE pathogenesis by decreasing immune complex clearance capacity. The literature is controversial in respect to mannose-binding lectin (MBL)[22,23] and antibodies against MBL[24] in the pathogenesis of SLE. Some authors, and this includes our group, have described the presence of increased MBL deficiency in SLE patients (unpublished data). However, further studies should be conducted for a better elucidation of this association with SLE.

Defects in immunoglobulin synthesis (antibody deficiencies)

Antibody deficiencies also referred as immunoglobulin deficiencies, represent a group of diseases (immune system disorders) characterized by low or absent levels of immunoglobulin in the blood. Immunoglobulins (Ig) are large y-shaped glycoprotein molecules produced by B cells that detect, bind and neutralize foreign substances (like bacteria, viruses, fungi, toxins and allergens). They also have the capability to signal immune cells to eliminate foreign substances. Antibody deficiencies represent a group of diseases and are considered the most common type of primary immune deficiencies in humans. Due to the fact that protective levels of IgG that are passively acquired by the newborns from the mother decreases during the first year of life, symptoms of this group of diseases only become symptomatic at the end of the first year of life. The spectrum of antibody deficiencies is broad, ranging from the absence of B cells and serum Igs (most severe type of antibody deficiency) to selective antibody deficiency with normal serum levels of total immunoglobulin. In addition to increased susceptibility to infections, clinical presentation of antibody deficiencies may also include other disease processes (e.g., autoimmunity and malignancies).

Common variable immunodeficiency disorders

Common variable immunodeficiency (CVID) is a heterogeneous group of primary antibody deficiencies diagnosed in humans, with broad clinical spectrum. CVID patients present history of hypogammaglobulinemia, recurrent respiratory tract infections, but the clinical spectrum may include autoimmune phenomena, bowel inflammatory or infectious disease, and granulomatous disease which can affect liver, spleen and lungs.[25] It has been postulated that persistent antigen stimulation, recurrent tissue damage, defective clearance of immune complexes and immune dysregulation contribute toward the development of autoimmunity, including SLE, but more frequently autoimmune cytopenia and endocrinopathy. Fernandez-Castro et al. described a series of 18 patients with SLE and CVID. Interestingly, up to 67% of them had the autoimmune disease controlled after the development of the immunodeficiency.[26] Genetic abnormalities described in CVID include defects in the inducible co-stimulator (ICOS), the membrane activator and calcium-modulator interactor (TACI), the B-cell activating factor receptor (BAFF-R), CD19, CD20 and CD81 (Table 2).[19] Although CVID has been described in patients after the diagnosis of SLE,[26,27] immunosuppressive agents used for SLE treatment can be the very cause of hypogammaglobulinemia development, turning the definitive diagnosis of CVID into a difficult task, since the diagnosis of CVID depends on exclusion of all other known causes of hypogammaglobulinemia.

Selective IgA deficiency

Selective IgA deficiency (SIgAD) is the most common PID (ranging from 1:400 to 1:3000).[9] Since the majority of patients are asymptomatic, this disorder may be unnoticed during childhood or even on adult phase. These patients present recurrent sino-pulmonary infections, allergy, gastrointestinal disease, endocrinopathy, malignancy and autoimmunity (Table 2). Eventually, patients with SIgAD evolve to CVID. SIgAD is frequently found in patients previously diagnosed with autoimmune disease such as Graves' disease (GD), type 1 diabetes (T1D), celiac disease (CD), myasthenia gravis (MG), SLE, and rheumatoid arthritis (RA).[28] A high prevalence of SIgAD was described in juvenile SLE (5.2%) and in adult onset SLE (2.6%).[8] It is hypothesized that the absence of mucosa IgA may reduce clearance and neutralization of antigen and pathogen,

Table 1 – Complement deficiencies associated with SLE or SLE-like manifestation.

Disease	Association features and autoimmune manifestation	Inheritance	Defective gene	OMIM number
C1q deficiency	SLE-like syndrome, rheumatoid syndrome, infections	AR	C1QA C1QB C1QC	120550 601269 120575
C1r deficiency	SLE-like syndrome, rheumatoid syndrome, multiple autoimmune diseases, infections	AR	C1r	216950
C1s deficiency	SLE-like syndrome; multiple autoimmune diseases	AR	C1s	120580
C4 deficiency	SLE-like syndrome, rheumatoid syndrome, infections	AR	C4A	120810
C2 deficiency	SLE-like syndrome, vasculitis, atherosclerosis, polymyositis, pyogenic infections; glomerulonephritis	AR	C2	217000
C3 deficiency	Life threatening pyogenic infections; SLE-like disease; glomerulonephritis; atypical hemolytic–uremic syndrome	AR	C3	120700
C5 deficiency	*Neisseria* infection, SLE	AR	C5α or C5β	120900
C6 deficiency	*Neisseria* infection, SLE	AR	C6	217050
C7 deficiency	*Neisseria* infection, SLE, vasculitis	AR	C7	217070
C8a deficiency	*Neisseria* infection, SLE	AR	C8α	120950
C8b deficiency	*Neisseria* infection, SLE	AR	C8β	120960
Factor I deficiency	Recurrent pyogenic infections, glomerulonephritis, SLE; hemolytic–uremic syndrome; severe pre-eclampsia	AR	*CFI*	610984

AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; SLE, systemic lupus erythematosus.

which serve as triggers for breaking immune tolerance. However, the association between SIgAD and SLE is not completely understood yet.

Hyper-IgM syndrome

Hyper-IgM syndrome (HIGM) is a non-classical PID characterized by antibody deficiency with the absence of IgG and IgA but normal or increased IgM levels. Different genetic mutations can cause this PID; including mutation of CD40 ligand gene (*CD40LG* gene, X-linked HIGM), *CD40* gene, Activation-induced DNA-cytidine deaminase gene (*AICDA* gene, also known as AID) and uracil DNA glycosylase gene (*UNG*) (Table 2).[19,29] Patients with HIGM usually present during childhood opportunistic infections and autoimmune diseases (autoimmune cytopenia, nephritis, inflammatory bowel disease, autoimmune hepatitis, arthritis, hypothyroidism and SLE). Autoimmune manifestation are more frequent in patients that present HIGM due to mutations in AID, however, autoimmune manifestations have also been reported in other types of HIGM.[29,30] There are very few cases reported on the coexistence of SLE and AID or UNG associated Hyper-IgM.[31]

Isolated IgG subclass deficiency

IgG subclass deficiency is defined as a serum IgG subclass level that is more than two standard deviations below the normal mean for age. IgG subclass deficiency can be associated with recurrent infections of the upper and lower respiratory tracts.[32] Pathogens are generally limited to bacteria and respiratory viruses. Because IgG2 is important in the response to polysaccharide antigens, IgG2 subclass-deficient patients typically have infections with *Haemophilus influenza* or *Streptococcus pneumoniae*.[33] In adults, deficiency of IgG3 subclass is the most common, whereas in children IgG2 is the most prevalent IgG subclass deficiency. IgG subclass deficiency may be seen in conjunction with other primary immune deficiency disorders, such as ataxia-telangiectasia and IgA deficiency.[34] An IgG subclass deficiency might occur as an isolated single IgG subclass deficiency or as a deficiency of two or more IgG subclasses. The literature describes sporadic cases of autoimmune manifestation in patients with IgG subclass deficiency,[35–38] like IgG1,[39] IgG4[40] and combined IgG2 and IgG4 subclass deficiency.[41] The prevalence might be higher, however those cases might go unnoticed, since IgG subclasses serum level determination is not included in routine evaluation of SLE patients. Jesus et al. (2011) also showed the coexistence of IgG2 deficiency in 5.5% of the juvenile SLE patients studied, representing 21% of all PID cases in their series.[18]

IgM deficiency

The IgM deficiency (IgMD) has been reported in patients with several forms of autoimmune diseases. One reported case describes a 15-year-old female presenting a 22q11.2 deletion syndrome (partial DiGeorge Syndrome) who presented recurrent and chronic otitis media, developmental delay, not associated with any other immunologic defects.[42] Patients with IgMD and 22q11.2 deletion syndrome may present sinopulmonary recurrent infections, which typically respond to conventional antibiotic therapy without the need of prolonged antibiotic use or intravenous immunoglobulin therapy (IVIg).[43] In IgMD patients, recurrent respiratory tract infections, asthma, allergic rhinitis, vasomotor rhinitis, angioedema, and anaphylaxis have been described.[44] Patients

Table 2 – Primary immunodeficiencies frequently associated with SLE or SLE-like manifestation.

Disease	Association features and autoimmune manifestation	Inheritance	Defective gene	OMIM number
Predominantly antibody deficiencies				
CVID	Hypogammaglobulinemia, recurrent chronic infections, inflammatory bowel disease, autoimmune hemolytic anemia, thrombocytopenia, rheumatoid arthritis, pernicious anemia, diabetes mellitus, polymyositis, SLE	AR	*ICOS*	604558
		AR	*CD19*	107265
		AR	*CD81*	186845
		AR	*CD20*	112210
		AD, AR	*TNFRSF13B* (TACI)	604907
		AR	*TNFRSF13C* (BAFF-R)	606269
SIgAD	Usually asymptomatic; may have recurrent infections with poor antibody responses to carbohydrate antigens, rheumatoid arthritis, diabetes mellitus, SLE	Variable	Unknown	
HIGM	Decreased IgG, normal to elevated IgM, sinopulmonary infections, lymphoid hyperplasia, diabetes mellitus, autoimmune hepatitis, rheumatoid arthritis, inflammatory bowel disease, uveitis, idiopathic thrombocytopenia purpura, autoimmune hemolytic anemia, SLE	XL	*CD40LG*	300386
		AR	*CD40*	109535
		AR	*AICDA*	605257
		AR	*UNG*	191525
Isolated IgG subclass deficiency	Reduction in one or more IgG subclass, usually asymptomatic; a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections	Variable	Unknown	
SIgMD[a]	Recurrent respiratory tract infections, asthma, allergic rhinitis, vasomotor rhinitis, angioedema, and anaphylaxis, glomerulonephritis, SLE		Unknown	
Congenital defects of phagocyte number, function or both				
CGD	Recurrent suppurative microbial infections, chronic inflammation with granuloma formation, inflammatory bowel disease, SLE	XL	CYBB	306400
		AR	*CYBA*	233690
		AR	*NCF1*	233700
		AR	*NCF2*	233710
		AR	*NCF4*	601488
Well-defined syndromes with immunodeficiency				
WAS	Thrombocytopenia with bleeding diathesis, eczema, recurrent infections, autoimmune hemolytic anemia, vasculitis, inflammatory bowel disease, glomerulonephritis, rheumatoid arthritis, SLE	XL	WAS	301000
Syndromes with autoimmunity				
APECED	Autoimmunity of parathyroid, adrenal, and other endocrine organs, chronic candidiasis, vitiligo, hepatitis autoimmune, diabetes mellitus	AR	*AIRE*	240300
ALPS-FAS	Splenomegaly, adenopathies, autoimmune cytopenias, lymphoma, defective lymphocyte apoptosis	AD, AR	*TNFRSF6*	601859
ALPS-FASLG	Splenomegaly, adenopathies, autoimmune cytopenias, defective lymphocyte apoptosis	AD, AR	*TNFSF6*	134638
ALPS-CASP10	Adenopathies, splenomegaly, autoimmunity, defective lymphocyte apoptosis	AD	CASP10	603909

Table 2 – (Continued)

Disease	Association features and autoimmune manifestation	Inheritance	Defective gene	OMIM number
Caspase 8 defect	Adenopathies, splenomegaly, recurrent bacterial/viral infections, defective lymphocyte apoptosis, hypogammaglobulinemia	AD	*NRAS*	164790
Others				
ICL[a]	$CD4^+$ lymphocytopenia, opportunistic infections, antiphospholipid syndrome, psoriasis, Hashimoto's thyroiditis, Graves disease, ulcerative colitis, vitiligo and SLE		*UNC119*	

AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; XL, X-linked inheritance; CVID, common variable immunodeficiency; SIgMD, selective deficiency IgM; SIgAD, selective deficiency IgA; HIGM, hyper-IgM syndrome; CGD, chronic granulomatous disease; WAS, Wiskott–Aldrich Syndrome; APECED, autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy; ALPS, autoimmune lymphoproliferative syndrome; ICL, idiopathic $CD4^+$ lymphocytopenia; SLE, systemic lupus erythematosus.

[a] Non-classic PID.

may present antinuclear antibodies (ANA).[45] Few reports have focused their analysis on selective IgM deficiency however a detailed pathogenesis of this disorder still remains to be carefully analyzed. A study on a case report of a 37-year-old woman who presented selective IgM deficiency with concurrent IgG4 deficiency, various dermal symptoms and a bronchial polyp, serves as an observation of a not very clear association between a solitary polyp and IgM deficiency, however suggestions have been made for repeated IgM deficiency-related airway infections as a probable etiological factor for the inflammatory polyp.[46] It is speculated that the reduction of secreted IgM production is related to the risk of progression of autoimmune diseases, such as autoimmune glomerulonephritis and SLE in humans. In fact, a few case reports or series show association of this disorder with autoimmune rheumatic diseases, including SLE,[44,47] especially in patients with disease of long duration.[48] Interestingly, disease remission did not correlate with elevation of IgM serum levels, indicating a deeper dysregulation of the immune system.

Congenital defects of phagocyte

Phagocytes such as monocytes/macrophages as well as granulocytes are the cells that engulf and destroy ingested pathogens during a process denominated phagocytosis. In certain conditions, either the number of phagocytes is reduced or their functional capacity is impaired.[49] Almost all PID due to phagocyte defects are a consequence of inherited mutations affecting the innate immune system. Most of these PID patients are identified at very young age based on their clinical phenotype of susceptibility to normally nonpathogenic bacteria or fungi, and in some cases, the infectious agents point to the disorder.[50] Defects of these cells include decreased number of neutrophils caused by defects on granulocyte development or capability to exit into the circulation leading to neutropenia; or due to the presence of autoantibodies or isoantibodies directed against neutrophil membrane antigens. Other defects include abnormalities in granulocyte killing ability, opsonic capability secondary to deficiencies of antibody and complement factors, and chemotaxis.[50]

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is a primary immunodeficiency of phagocytes, with X-linked or autosomal recessive inheritance. The X-linked form presents mutation in *CYBB* gene that encodes the heavy chain of cytochrome b_{558}, or gp91-phox (56% of cases), an electron transport protein responsible for the oxidative burst of phagocytes. These patients present severe and recurrent infections of skin, respiratory system, gastrointestinal tract and adjacent lymphonodes, pancreas, bones and central nervous system. Persistence of microorganisms in phagolysosomes leads to granuloma formation that causes obstruction along the gastrointestinal or urinary tract. In the autosomal recessive form, genes affected include the other components of NADPH oxidase system: *NCF1* (adapter protein p47-phox, 33% of cases); *NCF2* (activator protein p67-phox, 5% of cases); and *NCF4* (p40-phox), 6% of cases.[51] Patients with X-linked form present severe infections in the first year of life, and patients with the autosomal recessive form of CGD have less severe clinical manifestation, with late onset symptoms. Oral ulcers and autoimmune manifestation (antiphospholipid syndrome, recurrent pericardial effusion, juvenile idiopathic arthritis, IgA nephropathy, cutaneous and systemic lupus erythematosus, and autoimmune pulmonary disease) are frequently seen in patients with CGD.[52] Additionally, the mother's status of carrier of the affected gene is associated to higher frequency of discoid lupus lesions.[11] X-linked form can also present McLeod phenotype (a genetic disorder that may affect the blood, brain, peripheral nerves, muscle and heart, caused by a variety of recessively inherited mutations in the *XK* gene on the X chromosome, responsible for producing the Kx protein, a secondary supportive protein for the Kell antigen on the red blood cell surface, with compensated hemolysis, acanthocysis and progressive degenerative neuromuscular disorders).[53]

Well-defined PID and PID syndromes associated with SLE

Within the clinical framework of PID, the most common feature besides susceptibility to infections is represented by autoimmune manifestations. Recent advances in both fields have lead to the identification that associations of PID with AIDs are more frequent than previously appreciated.[5,54,55] It became evident that different types of PID display consistent associations with distinct autoimmune disorders (including homozygous deficiencies of early components of the classical Complement pathway, selective and partial immunoglobulin deficiencies, particularly isolated IgA and IgM deficiencies, and X-linked and autosomal forms of chronic granulomatous disease), allowing the perception that the study of the association between PID and AIDs represents a unique opportunity for new insights and a better understanding of the pathophysiology as well as the genetic basis of autoimmunity.

Wiskott–Aldrich syndrome

The Wiskott–Aldrich syndrome (WAS) is a PID caused by mutation in the WAS gene, that encodes a protein associated to the process of cell locomotion, immunological synapse formation, apoptosis and phagocytosis. Mutations in the WAS gene can lead to severe clinical manifestations (classical WAS), light manifestations (X-linked thrombocytopenia/XLT) and X-linked neutropenia (neutropenia and thrombocytopenia without myelodysplasia or immunodeficiency). Patients usually present elevated IgA and IgE serum levels, normal IgG, and slightly decreased IgM. The cytotoxic activity of NK cells and CD8 T lymphocytes is impaired. Infections are common since six months of age, with the development of otitis media, sinusitis, pneumonia and diarrhea. Viral infections are common, especially for chickenpox, *herpes simplex* and *molluscum contagiosum*. Clinical presentation is normally variable, with symptoms appearing soon after birth or in early life. Patients with WAS have small platelets, lacking specific granules, reduced numbers of organelles in the cytoplasm, defective platelet aggregation and ineffective thrombocytopoiesis. The appearance of petechiae, bruising, bleeding and severe cases of thrombocytopenia hemorrhage of central nervous system are frequent.[56,57] Eczema, recurrent infections, autoimmune diseases (hemolytic anemia, vasculitis, nephropathy, purpura resembling Henoch–Schonlein, inflammatory bowel disease, SLE, and IgA nephropathy) and malignancies (lymphoma, leukemia) are not rare manifestations.[13,58]

Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy

Autoimmune polyendocrinopathy candidiasis and ectodermal dystrophy (APECED) or autoimmune polyendocrine syndrome type I (APS1) is a PID that harbors autoimmunity within its very essence. There is a wide variation in the clinical features and course of APECED, even among patients sharing the same mutation in the autoimmune regulator gene (*AIRE*), involved in the disorder and whose encoded protein is responsible for presenting several self-antigens in thymus medullae. While specific mutations in the *AIRE* gene have not been associated with disease phenotype, associations with specific HLA haplotypes have been noted for some of the autoimmune manifestations of APECED, including alopecia, T1D, and Addison's disease. Chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenocortical failure are the classic triad of findings that characterize this syndrome.[59] Other autoimmune endocrinopathies can be present, including insulin-dependent diabetes mellitus, autoimmune thyroiditis, premature ovarian failure, and hypergonadotropic hypogonadism. Immune-mediated gastrointestinal diseases, autoimmune dermatologic conditions, ectodermal dystrophy, keratoconjunctivitis, iridocyclitis, hemolytic anemia, oral and esophageal cancers, chronic hepatitis, nephritis, cholelithiasis and SLE have also been seen associated to APECED.[60,61]

Autoimmune lymphoproliferative syndrome

Autoimmune lymphoproliferative syndrome (ALPS) is an autosomal dominant disorder caused by abnormalities in Fas-mediated lymphocyte apoptosis, with clinical features of splenomegaly and lymphadenopathy, and various autoimmune manifestations. ALPS caused by heterozygous mutations in the Fas gene (*TNFRSF6*; ALPS Type Ia) make up the majority of identified cases. ALPS caused by mutations in other factors involved in the Fas apoptosis pathway have been identified, including FasL (*TNFSF6*; ALPS Type Ib), Caspase 8 (*NRAS*) and Caspase 10 (*CASP10*) (the latter two, ALPS Type II). There is also a subgroup of patients with ALPS phenotype, abnormal Fas-mediated apoptosis, but no identified mutation in the Fas pathway (ALPS Type III).[62,63] Immunological abnormalities characteristic of ALPS include the presence of increased number of circulating $CD4^-CD8^-$ α/β^+ lymphocytes (double negative), as well as T- and B-cell lymphocytosis and polyclonal hypergammaglobulinemia. Autoimmune hemolytic anemia and immune thrombocytopenia are the most common autoimmune features seen in ALPS. Autoimmune neutropenia and the presence of anticardiolipin antibodies are also often present, whereas autoimmune hepatitis, uveitis, and glomerulonephritis are much less common manifestations in these patients.[63] The literature describes a case of SLE-like syndrome in a 59-year-old woman with arthritis, low fever, intermittent hypotension, confusion, macular skin rash with telangiectasia and perivascular lymphocyte infiltration, cytopenia without abnormal cells, hepatosplenomegaly, pericardial and pleural effusion, cervical lymph node enlargements and diffuse large B cell lymphoma. This patient was described with autoimmune lymphoproliferative syndrome-like syndrome.[15]

Idiopathic $CD4^+$ lymphocytopenia

Idiopathic $CD4^+$ lymphocytopenia (ICL) is a non-classical PID characterized by a T $CD4^+$ lymphocyte cell count below 300/mm^3 or 20% of total T lymphocyte cell count in the absence of identified cause, including human immunodeficiency virus (HIV) or human lymphocytotropic virus (HTLV) infections, and absence of causative drug.[64] Recently, a mutation in patients with ICL was described,[65] but further studies are needed for definitive conclusion since the etiology still remains poorly understood and inadequately defined. Mechanisms implicated in $CD4^+$ lymphocyte reduction may include decreased production, increased destruction, and tissue sequestration of these cells. Clinical presentation includes *Cryptococcus* spp. opportunistic infections and non-mycobacterial infections. Presence of malignancies is common, frequently due to opportunistic pathogens with an oncogenic potential (human papillomavirus/HPV, Kaposi's sarcoma by HHV8+).[66,67] Autoimmune diseases observed in a series of 39 cases of ICL include SLE, antiphospholipid syndrome, psoriasis, Hashimoto's thyroiditis, Graves disease, ulcerative colitis and vitiligo.[68,69]

Clinical characteristics of patients with SLE and PID manifestations followed by the outpatient clinic of the Rheumatology Division at Universidade Federal de São Paulo

Between 2009 and 2011, our group followed 315 consecutive adult SLE patients at the Rheumatology Division outpatient clinic of the University Hospital of Universidade Federal de São Paulo. The purpose of the study was to systematically track a comprehensive array of PID in a large cohort. Once the disease activity could influence the results, all patients were followed until achieving disease quiescence. Fifteen patients remained with active disease throughout the follow-up and were, therefore, excluded from the analysis. Patients followed were predominantly females (16 males and 284 females), with 39.58 ± 12.54 mean years-old (age ranging from 18 to 61 years), mean disease duration of 10.74 ± 8.15 years (disease duration from 1 to 53 years) and mean age at SLE onset of 28.79 ± 10.89 years-old (SLE onset from 3 to 69 years). Total frequency of infections in SLE patients was 28 (9.33%). Those patients were classified using the warning signals for primary immunodeficiency recently revised.[70] Unfortunately the cross-sectional design of our study could not allow the calculi of mortality rate. Nine patients had recurrent airway infections, whereas 15 presented recurrent urinary tract infections and three, skin furunculosis. Two patients presented recurrent oral/genital *Herpes simplex* and two others had *Herpes zoster* infection. Additionally, two patients manifested mycobacterial infection: one had pulmonary tuberculosis and the other hanseniasis (Table 3). In the present series, other autoimmune diseases were observed in 47 individuals (15.66%) [including rheumatic autoimmune diseases (*n* = 32) and non-rheumatic autoimmune diseases (*n* = 20)], some of which presenting more than one autoimmune condition. Eighty-four patients (28%) were identified with immunity defects compatible with classical PID (Table 3), and in four patients (1.3%) more than one associated PID were identified (SIgAD + IgG2; SIgAD + IgG4; IgMD + IgG2 in 2 patients). Differently from our results, the literature describes one case of SIgMD accompanied with IgG4 deficiency (Ideura et al.[46]). Interestingly, one patient presented a respiratory burst profile impaired enough to be classified as a CGD gene carrier but no patient presented the profile compatible with full-blown disease. Our clinical and laboratory findings have demonstrated that the PID observed in SLE patients are considered mild in terms of severity of infections and mortality. We speculate that those PID are compatible with apparently normal life, but that the consequent long-standing antigenic burden may be a risk factor for the development of AIDs, represented in this cohort by SLE. Generally, severe forms of PID are diagnosed at early stage of life, while non-severe or mild forms of PID manifestations are mostly asymptomatic.[20] We found that 28% of our cohort of adult SLE patients was constituted by mild PID which allowed a longer survival rate, passing unnoticed during childhood.

Table 3 – Autoimmune diseases, primary immunodeficiencies and infections found in 300 Brazilian SLE patients.

Autoimmune rheumatic disease n = 32 (10.6%)	
Antiphospholipid syndrome	*n* = 16 (5.3%)
Sjögren syndrome	*n* = 7 (2.3%)
Systemic sclerosis	*n* = 4 (1.3%)
Rheumatoid arthritis	*n* = 4 (1.3%)
Polymyositis	*n* = 2 (0.6%)
Psoriatic arthritis	*n* = 1 (0.3%)
Non-rheumatic autoimmune disease n = 20 (6.6%)	
Hypothyroidism	*n* = 15 (5%)
Psoriasis	*n* = 3 (1%)
Vitiligo	*n* = 3 (1%)
Primary biliary cirrhosis	*n* = 1 (0.3%)
IgA nephropathy	*n* = 1 (0.3%)
Primary immunodeficiency disease (Classical and non-Classical) n = 84 (28%)	
SIgMD[a]	*n* = 24 (8%)
SIgAD	*n* = 3 (1%)
Def IgG	*n* = 1 (0.3%)
Def IgG1	*n* = 5 (1.6%)
Def IgG2	*n* = 40 (13.3%)
Def IgG3	*n* = 24 (8%)
Def IgG4	*n* = 11 (3.6%)
CGD gene carrier	*n* = 1 (0.3%)
Infections n = 28 (9.33%)	
Airway infection	*n* = 9 (3%)
Urinary tract infection	*n* = 15 (5%)
Furunculosis	*n* = 3 (1%)
Herpes simplex	*n* = 2 (0.6%)
Herpes zoster	*n* = 2 (0.6%)
Tuberculosis	*n* = 1 (0.3%)
Hanseniasis	*n* = 1 (0.3%)

SIgAD, selective IgA deficiency; SIgMD, selective IgM deficiency.
[a] Non-classic PID.

This could possibly explain the absence of illnesses such as CVID, CGD and HIGM. Surprisingly, in our cohort the presence of IgMD, a non-classical form of PID, was very frequent. We also observed in our cohort a large number of SLE patients with IgG subclass deficiency, while literature reports only some cases of isolated deficiency of IgG2 and IgG4.[18,41,71,72] In our study, all patients with IgG4 deficiency and 75% of those with IgG3 deficiency had lupus nephropathy, which is above the ∼50% frequency in the whole cohort. In addition, patients with IgMD presented lower frequency of oral ulcers. Apart from IgG4 and IgG3 deficient patients, the remaining patients did not present a much severe phenotype regarding the presence of infections and lupus manifestations.

Our findings regarding the association of immunoglobulin deficiency and the development of autoimmune disease could be partially explained based on the 'waste disposal' hypothesis, which postulates that defects on the clearance of dying cells increases the risk of developing autoimmunity since these cells provide the source of auto antigens responsible for driving autoantibody production in SLE.[7] Additionally, because SLE is associated with a humoral exacerbated response, the presence of a primary dysfunction of B lymphocytes may be considered as a predisposing factor for unbalanced IgG subclasses synthesis, which may be considered as a factor for the development of SLE. These results suggest that mild immunologic defects might be compatible with patient survival, but at the expense of some chronic overload and future consequences to the immune system, which could lead to the development of immune disorders characteristic of SLE in the adulthood. The study findings give ground to further investigations that could deeply explore the participation of PID in the pathogenesis of SLE and other autoimmune rheumatic and non-rheumatic disease.

Conclusion

PID are a group of monogenic diseases in which mutations of certain genes can lead to increased susceptibility to infections but may also result in loss of central and/or peripheral tolerance. Therefore, AIDs are common among patients with a diverse array of PID. Immunoglobulin deficiency forms a peculiar group of PID, in which the inheritance appears to be polygenic and there is a wide severity spectrum, with mild forms that usually remain unnoticed. Our findings in adult patients with SLE suggest that AIDs can present a higher frequency of less severe forms of PID without severe infections. The presence of some forms of PID was associated with certain phenotypic peculiarities in SLE patients. The literature and our findings show that PID and AIDs frequently coexist and patients with autoimmune diseases should be carefully monitored for the presence of PID and vice versa.

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Conflicts of interest

The authors declare no conflicts of interest.

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