Autoimmune manifestations in primary immune deficiencies

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A B S T R A C T

Autoimmune manifestations have long been perceived as paradoxical in patients with primary immune deficiencies (PID). However, a defect in the mechanisms of control of self-reactive B and T cells may favour these manifestations.

Three PID are defined by the occurrence of autoimmune manifestations: APECED (Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy), autoimmune lymphoproliferative syndrome (ALPS) and IPEX syndrome (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). In these conditions, organ specific autoimmune diseases such as type 1 diabetes mellitus or Hashimoto's thyroiditis are prominently encountered.

Several other PID such as common variable immunodeficiency (CVID), Good syndrome and hyper-IgM syndrome are associated with a wide variety of autoimmune manifestations, mainly autoimmune cytopenias. Thus, autoimmune manifestations have been reported in 22% of patients with CVID, increasing to 50% in the subgroup of patients with systemic granulomatosis. Complement deficiencies involving components of the classical pathway are associated with systemic lupus erythematosus (SLE). Homozygous C2 deficiency, which is the most frequent hereditary deficiency in complement classical pathway components, is associated with SLE in 10% of the cases. Complete C1q and C4 deficiencies are less frequent but associated with a higher prevalence of SLE.

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1. Introduction

More than one hundred primary immune deficiencies (PID) have been identified so far. Although PID favour the occurrence of infections in most of the cases, many other clinical manifestations may occur in these patients including autoimmune manifestations [1,2]. Autoimmunity has long been perceived as paradoxical in patients with PID. However, PID may result in a defect in the mechanisms of control of self-reactive B and T cells and favour the occurrence of autoimmune manifestations. Three types of PID are defined by the occurrence of autoimmune diseases, whereas autoimmune manifestations may occur in others with a variable frequency.

2. Primary immune deficiencies defined by the occurrence of autoimmune manifestations

2.1. APECED syndrome

APECED (Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy) syndrome is a recessive autosomal disease defined by at least two of the following symptoms: chronic cutaneous-mucous candidiasis, hypoparathyroidism and Addison disease [3]. Candidiasis is usually the first clinical manifestation of the disease, occurring around the age of 5, followed in most cases by hypoparathyroidism before the age of 10 and adrenocortical failure before the age of 15. Other organ-specific autoimmune manifestations encountered in this condition include hypothyroidism, hypogonadism, type 1 diabetes mellitus, autoimmune hepatitis, pernicious anemia, vitiligo, alopecia, primary biliary cirrhosis and ectodermal dysplasia.

APECED syndrome results from a defect in the autoimmune regulator (AIRE) gene [4]. AIRE is involved in the expression of a variety of peripheral tissue antigens in medullary epithelial cells of the thymus [5]. In healthy individuals, AIRE increases the transcription of these antigens and allows the negative selection of self-reactive T cells leading to their deletion. Mice deficient in AIRE also show evidence of spontaneous organ-specific autoimmunity [6].

2.2. Autoimmune lymphoproliferative syndrome

Autoimmune lymphoproliferative syndrome (ALPS) is characterized by the occurrence of lymphadenopathy, splenomegaly and hyperlymphocytosis with circulating CD4+/CD8− double negative T cells. Lymphoproliferation is associated with polyclonal hypergammaglobulinemia and autoimmune cytopenias. The diagnosis is usually made at the age of 2. These patients may develop autoantibodies usually associated with systemic lupus erythematosus (SLE) without evidence of clinical manifestations of SLE.

In patients with ALPS, autoimmune manifestations occur in 50 to 70% of the cases, mainly in the form of autoimmune cytopenias [7]. In these patients, autoimmune haemolytic anemia (AIHA), idiopathic thrombocytopenic purpura (ITP) and autoimmune neutropenia occur in 29–38%, 23–34% and 19–27% of the cases, respectively [8,9]. These cytopenias are usually severe and become more severe with age. Other autoimmune manifestations of proven or suspected autoimmune mechanisms have been reported less commonly: glomerulonephritis, optic neuritis, Guillain-Barré syndrome, arthritis, cutaneous vasculitis [10], primary biliary cirrhosis, autoimmune hepatitis [11], blistering dermatosis [12] or acquired factor VIII deficiency [13]. Autoantibodies are frequently detected in the serum of patients with ALPS but there is a poor correlation between detection of autoantibodies and related clinical manifestations, probably at least in part because most of these patients present with major hypergammaglobulinemia.

2.3. IPEX syndrome

IPEX syndrome (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) is a rare disease, described in 1982 and due to a mutation in the Foxp-3 gene [14], resulting in the defective development of CD4+ CD25+ regulatory T cells [15]. As a consequence, T cell activation and cytokine production are increased. Disease manifestations are characterized by autoimmune enteritis, type 1 diabetes mellitus occurring during the first months of life, eczema, hypothyroidism, AIHA, membranous nephropathy and recurrent infections. Patients presenting with IPEX syndrome usually die before the age of 2 [14].

3. Other primary immune deficiencies associated with autoimmune manifestations

PID with defective antibody production, such as common variable immunodeficiency (CVID), Good syndrome or hyper-IgM syndrome (HIGM) are often associated with autoimmune manifestations. Since these patients are hypogammaglobulinemic, the search for autoantibodies is usually negative.

3.1. Common variable immunodeficiency

CVID is the most frequent symptomatic PID in the adult. Several genetic defects have been described among CVID patients: inducible costimulator (ICOS) [16], CD19 [17], transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) [18] or B-cell activating factor of the tumor necrosis factor family receptor (BAFF-R) [19] deficiencies.

Clinical manifestations usually occur between 20 and 30 year old, although the disease can occur later in life [20]. Disease manifestations are very heterogeneous and associate infections, systemic granulomatosis, autoimmune manifestations, lymphoproliferation and gastrointestinal disease. Biological analyses reveal hypogammaglobulinemia, a normal B cell count in most of the cases and a variable T cell phenotype [21].

Autoimmune manifestations occur in about 22% of CVID patients [20,22] (Table 1). They are more frequent among women and among patients with granuloma, increasing to 50% of patients in the latter case. Autoimmune diseases are organ specific in most of the cases, consisting in autoimmune cytopenias, pernicious anemia, Hashimoto’s thyroiditis, rheumatoid arthritis and/or vitiligo. In patients with CVID, ITP frequently precedes other clinical manifestations [20]. However, cytopenias may also occur later in the disease course.

3.2. Good syndrome

Good syndrome associates benign thymoma and severe immunodeficiency, with major B cell depletion, hypogammaglobulinemia and CD4+ T lymphocyte deficiency. As a consequence,
patients develop severe infections mainly due to intracellular pathogens. Autoimmune cytopenias, including neutropenia and/or thrombocytopenia, may also occur in this condition. Patients are usually older and have a worse prognosis than those with CVID [23].

3.3. Hyper-IgM syndrome

Hyper-IgM syndrome (HIGM) is characterized by an absence of IgG and IgA whereas IgM level is normal or increased. Several genetic abnormalities can cause HIGM: mutation of CD40 ligand (X-linked HIGM) [24], CD40 [25], NF-κB essential modulator (NEMO) [26], activation induced cytidine deaminase (AID) [27] or uracil DNA glycosylase (UNG) [28] genes. Self-reactive IgM repertoires of patients with HIGM differ significantly from those of healthy donors [29]. The diagnosis of HIGM is usually made during childhood and patients are exposed to opportunistic infections and autoimmune diseases, such as autoimmune cytopenias, nephritis, inflammatory bowel diseases, autoimmune hepatitis, arthritis, hypothyroidism and SLE [30]. Autoimmune manifestations are more frequent in patients with HIGM due to mutations in AID and NEMO genes [30] but have also been reported with other types of HIGM (Table 2). About 25% of AID deficient patients develop autoimmunity.

3.4. Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome (WAS) is an X-linked PID that usually associates eczema and thrombocytopenia. Autoimmune and inflammatory manifestations occur among 40 to 72% of the cases [31,32], and most of them develop more than one autoimmune manifestation. AIHA is the most frequent of these manifestations. Patients with WAS can also develop autoimmune neutropenia and inflammatory manifestations including arthritis, vasculitis, uveitis, inflammatory bowel disease and/or renal disease.

3.5. Idiopathic CD4+ lymphocytopenia

Idiopathic CD4+ lymphocytopenia (ICL) is characterized by a CD4+ T cell count of less than 300/mm³ or 20% of the total T cell count on more than one occasion in the absence of identified cause of lymphocytopenia including human immunodeficiency virus (HIV) or human T lymphocytotropic virus (HTLV) infections, other causes of immune deficiency and in the absence of a causative drug [33]. Zonios et al. recently reported a series of 39 patients with ICL [33]. The most frequent infections at diagnosis were Cryptococcus neoformans, human papillomavirus (HPV) and atypical mycobacterial infections. Nine patients presented autoimmune manifestations either before ICL was identified or during the follow-up: three had SLE, two had antiphospholipid syndrome (one of these two had also psoriasis and Hashimoto’s thyroiditis), one had Graves disease, AIHA, ulcerative colitis and vitiligo.

4. Autoimmune manifestations associated with hereditary complement deficiencies

Complement components deficiencies, especially in classical pathway components, lead to an increased susceptibility to SLE [34]. C1q, C1s and C1r complete deficiencies are rare and associated with a high risk to develop pediatric SLE. More than 90% of homozygous C1q deficient patients present with SLE-like syndrome [35], whereas SLE occurs in more than 50% of patients with C1s and/or C1r deficiencies [36].

Homozygous C2 deficiency, which is the most frequent hereditary deficiency in classical pathway complement components (1/10000 to 1/30000 among Caucasian people), is associated with SLE in 10 to 30% of the cases [36]. The genetic defect is the more often a deletion in intron 6, which leads to a premature stop codon in exon 7 with failure to synthesize the protein. SLE is as severe as SLE occurring among patients

<table>
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AID: activation induced cytidine deaminase; HIGM: hyper-IgM syndrome; NEMO: NF-κB essential modulator.
without complement deficiency and starts usually in adulthood. In a recent series of 45 patients with homozygous C2 deficiency, 12 had SLE, with a mean age of 37 years at diagnosis [37]. In addition, five patients had undifferentiated connective tissue disease and/or incomplete SLE. Three patients had vasculitis that was biopsy proven in two and associated with anti-neutrophil cytoplasm antibodies specific for anti-PR3 in one of these two. About 1 to 2% of Caucasian people have a heterozygous C2 deficiency and no higher risk of autoimmune disease has been reported in this case.

Finally, complete C4 deficiency is exceptional (about 25 reported cases) but associated with a high prevalence of 75% of SLE [34]. Complete C4A or C4B deficiencies are more frequent. Several studies reported an association between homozygous C4A deficiency and susceptibility to SLE [34] whereas homozygous C4B deficiency was not associated with an increased risk of developing SLE.

5. Conclusion

Autoimmune manifestations are frequent and often multiple in patients with PID. The diagnosis of PID should be made early in disease evolution since it may influence the therapeutic strategy. Autoimmune manifestations can help the clinician to make the diagnosis of PID, as well as in patients with recurrent infections, the type of infectious agent can help to diagnose the genetic defect responsible for PID.

Take-home messages

• More than one hundred primary immune deficiencies (PID) have been identified so far.
• The incidence of autoimmune diseases is increased in patients with PID.
• APECED, autoimmune lymphoproliferative syndrome and IPEX syndrome are defined by the occurrence of autoimmune diseases.
• Several other PID, including common variable immunodeficiency, Good syndrome and hyper-IgM syndrome, are associated with a wide range of autoimmune manifestations.
• Autoimmune cytopenias, particularly autoimmune haemolytic anaemia and idiopathic thrombocytopenic purpura are frequently encountered in PID patients.
• Susceptibility to systemic lupus erythematosus is increased in patients with classical pathway complement components deficiencies.

References

Transforming growth factor-beta-induced CD4+CD25+ regulatory T cells in vitro reverse and prevent a murine lupus-like syndrome of chronic graft-vs-host disease

It is yet unknown how to obtain enough peripheral Tregs, and how to make them effective in ameliorating a murine lupus-like syndrome of chronic graft-vs-host disease (cGVHD). This study, Su H. et al. (Br J dermatol 2008; 158:1197-209) was designed in order to confirm the contribution of transforming growth factor (TGF-beta1) in the function of CD4+CD25+ Tregs in vitro, and to identify in vivo suppressive effects of different Tregs generated through TGF-beta1.Suppressive effects of freshly isolated CD4+CD25+ Tregs, TGF-beta1-expanded Tregs (eTregs) and TGF-beta1-induced Tregs (iTregs) in vitro were assessed. Reverse transcription-polymerase chain reaction was used to detect Foxp3. The respective roles that different Tregs might play in controlling murine lupus-like syndrome of cGVHD were analyzed. TGF-beta1 was necessary for expanding the existing CD4+CD25+ Tregs in vitro, as well as converting peripheral CD4+CD25– T cells to CD4+CD25+ Tregs through up-regulating CD25 and Foxp3. These eTregs and iTregs had a suppressive effect similar to that of freshly isolated CD4+CD25+ Tregs. The inhibitory function of iTregs could be partially blocked by anti-TGF-beta1. Importantly, it was revealed for the first time that both eTregs and iTregs had an inhibitory effects on reversing the morbidity of mice that had already developed anti-dsDNA, and iTregs gave more suppression than eTregs. Besides, iTregs could prevent the onset and slow the progress of disease in a significantly dose–dependent manner. This indicates that TGF-beta1 signaling is required to maintain the suppression of CD4+CD25+ Tregs in vitro and in vivo. Together, this study suggests a possible therapeutic role for iTregs in the treatment of murine lupus-like syndrome of cGVHD.

Prevalence and clinical significance of anticomplement, anti-beta2-glycoprotein-1, and anti-heat shock Protein-70 autoantibodies in sudden sensorineural hearing loss

Sudden sensorineural hearing loss (SSNHL) is frequently classified as “idiopathic” since the causative factor responsible for its onset is not identified in most cases. In the present study, Gross M. et al. (Audioiology 13: 231-8) determined whether SSNHL is clinically associated with serum anti-heat shock protein-70 (anti-HSP70) and antiphospholipids (anti-PLs) autoantibodies and whether these autoantibodies have an impact on the prognosis of SSNHL. Sera from 63 patients with SSNHL were screened prospectively for the presence of anti-HSP70 and anti-PLs autoantibodies. (anti-cardiolipin, and anti-beta2-glycoprotein-1 antibodies. Demographic, Clinical, and audiometric variables were analyzed to find the possible role of serum autoantibodies in SSNHL patients. Sixteen patients (24.4%) had demonstrable anti-HSP70 antibodies and twenty one (33.3%) showed a positive result for at least one isotype (IgM or IgG) of anti-PLs. In 19% of the patients, anti-HSP70 and anti-PLs antibodies were positive in two combinations. A statistically significant association was found between anti-HSP70 antibodies and the Siegel recovery grade subgroup. SSNHL patients who were positive for anti-HSP70 antibodies showed a significantly higher rate of complete recovery and incomplete but partial recovery than SSNHL patients without anti-HSP70 antibodies (p=0.049), statistically significant association was found between total anticardiolipin, total anti-beta2-glycoprotein-1, total anti-PLs, and total anti-PLs in combination with anti-HSP70 antibodies and age (p=0.022). The present study confirms and supports previous studies regarding the association between anti-HSP70 and anti-PLs antibodies with SSNHL, and is the first to identify a positive association between anti-HSP70 antibodies and a positive outcome of SSNHL.

Predictors of premature gonadal failure in patients with systemic lupus erythematosus. Results from LUMINA, a multiethnic US cohort

To examine the predictors of time to premature gonadal failure (PGF) in patients with systemic lupus erythematosus (SLE) from LUMINA, a multiethnic US cohort. Gonzalez LA. et al. (Ann Rheum Dis 67: 1170–3). Factors associated with time to PGF occurrence were examined by univariable and multivariable Cox proportional hazards regression analyses: three models according to cyclophosphamide use, at T0 (model 1), over time (model 2) and the total number of intravenous pulses (model 3). Thirty-seven of 316 women (11.7%) developed PGF (19 Texan-Hispanics, 14 African-Americans, four Caucasians and no Puerto Rican-Hispanics). By multivariable analyses, older age at T0 (hazards ratio (HR) =1.10–1.14; 95% CI 1.02–1.05 to 1.19–1.23) and disease activity (Systemic Lupus Activity Measure-Revised) in all models (HR =1.22–1.24; 95% CI 1.10–1.12 to 1.35–1.37), Texan-Hispanic ethnicity in models 2 and 3 (HR =4.06–5.07; 95% CI 1.03–1.25 to 15.94–20.47) and cyclophosphamide use in models 1 and 3 (1–6 pulses) (HR =4.01–4.65; 955 CI 1.55–1.68 to 9.56–13.94) were predictors of a shorter time to PGF. Thus, disease activity and Texan-Hispanic ethnicity emerged as predictors of a shorter time to PGF while the associations with cyclophosphamide induction therapy emerged as an important determinant of PGF.