Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies

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Background: Primary immunodeficiencies (PIDs) are inherited diseases associated with a considerable increase in susceptibility to infections. It is known that PIDs can also predispose to cancer and immune diseases, including allergy, autoimmunity, and inflammation.

Objective: We aimed at determining the incidence of autoimmunity and inflammation in patients with PIDs.

Methods: We have retrospectively screened 2183 consecutive cases of PID in the Centre de Référence Déficits Immunitaires Héréditaires registry (CEREDIH; the French national PID registry) for the occurrence of autoimmunity and inflammation.

Results: One or more autoimmune and inflammatory complications were noted in 26.2% of patients, with a risk of onset throughout the patient's lifetime. The risk of autoimmune cytopenia was at least 120 times higher than in the general population, the risk of inflammatory bowel disease in children was 80 times higher, and the risk of other autoimmune manifestations was approximately 10 times higher. Remarkably, all types of PIDs were associated with a risk of autoimmune and inflammatory complications, although the greatest risk was associated with T-cell PIDs and common variable immunodeficiency. The occurrence of autoimmune disease is a negative prognostic factor for survival.

Conclusions: Our results provide the basis for a detailed prospective evaluation of autoimmunity and inflammation in the context of PIDs, with a view to accurately assessing these risks and describing the possible effect of medical intervention. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *Primary immunodeficiencies, autoimmunity, inflammation*

Primary immunodeficiencies (PIDs) are inherited disorders that result in impaired immune responses. Based on national or continent-wide registries, the prevalence of PIDs is currently estimated to be around 4 to 10 per 10^5 live births.[1-6] Many distinct syndromes have been described as a consequence of functional impairment of the innate and/or adaptive arms of the immune system. The development of genomic tools has led to the discovery of up to 300 genes in which mutations cause PIDs.[7] PIDs profoundly modify life expectancy and quality of life, primarily because of increased susceptibility to infections, which can be broad or

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Abbreviations used
CEREDIH: Centre de Référence Déficits Immunitaires Héréditaires (French national PID registry)
CVID: Common variable immunodeficiency
HSCT: Hematopoietic stem cell transplantation
PID: Primary immunodeficiency

restricted. Furthermore, it has long been known that patients with PIDs can be prone to cancers[5,8,9] and immune diseases, such as allergy,[10] inflammation, and autoimmune diseases.[11-13] Indeed, these manifestations are sometimes even part of the initial description of the disease, such as Wiskott-Aldrich syndrome[14] and chronic granulomatous disease.[15]

Although the occurrence of autoimmunity in various forms of PIDs (primarily common variable immunodeficiency [CVID][16,17]) has been widely reported, to the best of our knowledge, the incidence and types of autoimmune and inflammatory manifestations in patients with PIDs have never been surveyed.

Here we decided to retrospectively screen the Centre de Référence Déficits Immunitaires Héréditaires registry (CEREDIH; the French national PID registry)[3] for autoimmune and inflammatory disorders encountered in the latest 2183 patients for whom data are available.

The survey's main objectives were to estimate the overall frequency of these manifestations, identify at least some associated risk factors, and assess the manifestations' influence on overall survival. The present retrospective study might serve as the basis for a detailed prospective analysis of the medical interventions of value in preventing and/or treating the autoimmune and inflammatory complications of PIDs.

METHODS

We systematically screened patients with PIDs living in France for the occurrence of autoimmune or inflammatory complications (see Table E1 in this article's Online Repository at www.jacionline.org). Data were consecutively collected between September 1, 2013, and February 1, 2016, on 2183 patients either on initial registration in the CEREDIH database (hosted by the secured online ESID Registry, see www.esid.org) or during follow-up of previously registered patients.[3] All of the data were retrospectively collected within the CEREDIH French national registry. Information on new cases and follow-up were retrieved on a regular basis by CEREDIH staff, who visit the centers and have access to patients records. This starts from September 1, 2013, to February 1, 2016, which was when information on autoimmunity was collected in addition to the previously established data set.

The study population did not differ from the overall CEREDIH registry population (n = 5952) in terms of age or sex. There were slight differences in the proportions of subjects with innate PIDs and T-cell PIDs other than severe combined immunodeficiency or combined immunodeficiency (see Table E2 in this article's Online Repository at www.jacionline.org). The types of autoimmune/inflammatory complications and the date or age at onset were recorded, when available. Manifestations occurring after allogeneic hematopoietic stem cell transplantation (HSCT) were not included in the analysis. The database was approved by the French National Data Protection Commission (Commission Nationale Informatique et Libertés). The study procedures (analysis of the CEREDIH registry) were approved by the French National Consultative Committee on Data Processing in Healthcare Research (Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé; reference 06.327; dated September 7, 2006). Among many variables, the CEREDIH database contained information on the patient's date of birth, place of residence, clinical diagnosis, molecular diagnosis, allergy status, cancer status, and type of treatment (ie, immunoglobulin replacement therapy or HSCT).

Continuous variables are quoted as medians or means (ranges). In survival analyses we used the Kaplan-Meier nonparametric model to estimate the time to event. The threshold for statistical significance was set to a P value of less than .05 in all analyses. Statistical analyses were performed with R software (version 3.2.3).[18]

RESULTS

Overall frequency and distribution of autoimmune and inflammatory conditions

Of the 2183 surveyed patients (median age, 20 years; mean age, 25.8 years; range, 0.5-92 years), 571 (26.2%) had at least 1 autoimmune or inflammatory condition. The wide range of manifestations (n = 852) encompassed most of the known autoimmune diseases (Tables I and II and see Table E1), with the notable predominance of autoimmune cytopenia (mostly anemia, n = 110 manifestations), thrombocytopenia (n = 130 manifestations), or both. When comparing the study population with the general population in Western Europe,[19-25] we observed a marked increase in relative risk reaching 3- to 14-fold. The increase was particularly marked for autoimmune cytopenia (120-fold, Table III).[19-30] The relative risks are high in the pediatric population, as illustrated by the 830-fold increase risk for autoimmune hemolytic anemia, the 80-fold increased risk of inflammatory bowel disease, and the 40-fold increased risk of arthritis among children with PIDs compared with control French cohorts.[26-30] As shown in Table IV, 31.6% of the affected patients had experienced more than 1 autoimmune or inflammatory manifestation. These manifestations occurred throughout the patient's lifetime because the cumulative incidence plot was almost linear after the first 8 to 10 years of life (Fig 1; and see Fig E1 in this article's Online Repository at www.jacionline.org). Forty percent of patients had been affected by age 50 years.

Risk of autoimmunity and inflammation as a function of PIDs

When considering patients with PIDs with increased susceptibility to infections (ie, after excluding patients with an isolated hemophagocytic lymphohistiocytic syndrome [n = 64, with 2 cases of autoimmunity]) or a PID characterized by autoimmunity and lymphoproliferation in the absence of significant infections (ie, autoimmune lymphoproliferative syndrome; autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy; immune dysfunction, polyendocrinopathy, enteropathy, X-linked syndrome; and cytotoxic T lymphocyte–associated antigen 4 deficiency and gain-of-function mutations of signal transduce and activator of transcription 3 [n = 108, 73 cases of autoimmunity), the risk of autoimmunity/inflammation was 24.6% (496/2011) and thus did not differ from the risk in the overall study population. It is striking to note that all groups of patients classified as having B-cell CVIDs, other B-cell PIDs, T-cell PIDs, or innate immune system deficiencies were at risk of autoimmune or inflammatory manifestations (Table V and see Table E3 in this article's Online Repository at www.jacionline.org). CVID and combined immunodeficiencies were associated with the highest risk. It is noteworthy that 25% of patients with innate PIDs had autoimmune or inflammatory manifestations (eg, those with