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;140:1388-93.)

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

TABLE I. Categorization of the 852 autoimmune or inflammatory manifestations observed in 571 patients with PID

	No.	Percent
Autoimmune cytopenia	269	31.4
Gastrointestinal disorders	208	24.4
Skin	120	14.1
Rheumatologic disorders	109	12.8
Endocrine disorders	69	8.1
Lung	30	3.5
Eye	14	1.7
Kidney	11	1.3
Vasculitis and other systemic disorders	9	1.0
Neurologic disorders	8	1.0
Urologic disorders	3	0.4
Other	2	0.3
Total	852	

TABLE II. Number of patients with the most common autoimmune and/or inflammatory manifestations as a function of the type of PID

		Cytopenia, no. (%)*	Rheumatologic manifestations, no. (%)*	Gastrointestinal manifestations, no. (%)*
B-cell CVIDs	n = 408	68 (16.6)	22 (5.4)	39 (9.5)
Other B-cell deficiencies	n = 585	23 (3.9)	25 (4.3)	24 (4.1)
T-cell deficiencies	n = 845	117 (13.8)	37 (4.4)	63 (7.3)
Innate deficiencies	n = 324	9 (2.8)	16 (5.0)	50 (15.5)
Total	2162	217 (10)	100 (4.6)	176 (8.1)

Note, some patients had more than 1 type of autoimmune or inflammatory manifestation, and therefore the total number might exceed the total number of patients. Likewise, the sum of the percentages can exceed 100%.
*Based on the total number of patients with at least 1 autoimmune or inflammatory manifestation (n = 571).

chronic granulomatous disease). When considering age at onset, these manifestations occurred earlier in life in patients with T-cell and innate immune deficiencies than in patients with B-cell PIDs. The frequencies in these groups tended to converge at a value of greater than 40% in patients 50 years of age and older (Fig 2). As shown in Table E4 in this article's Online Repository at www.jacionline.org, cytopenia and rheumatologic manifestations were more frequently associated with T-cell PIDs than with other PIDs. We performed a univariate analysis of risk factors associated with the occurrence of autoimmunity/inflammation in patients with PIDs. Cancer and allergy (see Table E5 in this article's Online Repository at www.jacionline.org), but not sex, were apparently associated with autoimmunity (Table V). Allergy was the only independent risk factor in an adjusted Cox model analysis (Table VI). Early onset of infections, as well as treatment modalities (ie, immunoglobulin substitution) did not affect frequency (not data shown).

Influence on survival

Overall survival time was found to be significantly shorter in patients with PIDs with autoimmune/inflammatory manifestations than in those without these manifestations (Fig 3). This difference in survival was also observed when analyzing subgroups with CVIDs, other B-cell PIDs, and T-cell PIDs but not innate PIDs (see Fig E2 in this article's Online Repository at www.jacionline.org). Because patients with the most severe forms of PIDs tend to undergo allogeneic HSCT (n = 380 in the present study), we looked at whether the occurrence of autoimmune or inflammatory manifestation before transplantation had an effect on survival after HSCT. As shown in Fig 4, pre-HSCT autoimmunity/inflammation was associated with worse survival.

DISCUSSION

The present retrospective study is the first to report the frequency and distribution of autoimmune and inflammatory manifestations in a group of patients with PIDs. The study's nature (ie, retrospective and cross-sectional) was associated with some obvious limitations, despite the fact it is supported by a national registry. Given the importance of providing optimal care for patients with PIDs, our present results should be viewed as an incentive to launch a prospective analysis of autoimmunity in a large group of patients with PIDs. Despite this caveat, the present study based on the French CEREDIH PID registry produced some important findings: (1) autoimmunity/inflammation was observed in a large minority (26.2%) of patients with PIDs, (2) a wide range of manifestations were observed, (3) these manifestations occurred throughout the patient's lifetime, (4) virtually all PIDs are associated with an increased risk of autoimmunity/inflammation, and (5) autoimmune/inflammatory manifestations have prognostic significance.

Our results demonstrate that autoimmune and inflammatory diseases are much more frequent by a factor of at least 10 in patients with PIDs than in the general population. This increase in risk is extremely high (by a factor of 120) for autoimmune cytopenia (including both anemia and thrombocytopenia), inflammatory bowel disease, or arthritis in children.[19,26-30] This finding suggests that patients with autoimmune anemia, thrombocytopenia, or both should be screened for PIDs, ideally, but perhaps not exclusively during childhood. For instance, one can estimate that when there is in France 360 pediatric cases of autoimmune anemic ($12\ M \times 3 \times 10^{-5}$), there will be 50 PID cases (2000 children with PIDs $\times$ 2.5 10^{-2}) and therefore 15%. The same holds true for the occurrence of inflammatory bowel disease and perhaps inflammatory arthritis in children. The fact that almost the entire spectrum of autoimmune diseases can be observed in patients with PIDs obviously suggests the operation of many different underlying mechanisms. It is noteworthy that with the exception of autoimmune cytopenia, organ-specific autoimmunity and systemic autoimmunity, autoantibody-mediated autoimmunity, and T cell–mediated autoimmunity were all occurring in this group of patients with PIDs. It is difficult to understand why autoimmune cytopenia is so predominant notably but not exclusively in the setting of T-cell immunodeficiencies. It remains to be seen whether the abundance and spreading of self-antigens expressed by blood cells and related self-reactive T- and B-cell clones have a role. It would be interesting to assess the proportions of self-reactive B cells that target red blood cell or platelet self-antigens in patients with PIDs versus healthy subjects.

TABLE III. The relative risk of autoimmune disease in patients with PID

	Prevalence per 1 × 10^5 patients with PIDs	Prevalence per 1 × 10^5 of the general population	Relative risk
Cytopenia	12,000	100	120
Autoimmune hemolytic anemia (children, France)†	2,500	3	830
Immune thrombocytopenia (France)‡	6,000	100	60
Rheumatologic disorders*	5,000	860	6
Rheumatoid arthritis (children, France)§	800	20	40
Inflammatory bowel disease (adults, France)‖	7,800	180	43
Inflammatory bowel disease (children, France)‖	5,500	70	80
Skin*	6,000	600	10
Endocrine disorders*	3,000	1,000	3
Eye*	700	100	7
Kidney*	500	63	8
Vasculitis and other systemic disorders*	250	17.5	13
Neurologic disorders*	400	130	3

Items in brackets refer to the control population.
*Hayter and Cook,[19] Cooper and Stroehla BC,[20] Cooper et al,[21] Ramos-Casals et al,[22] Ji et al,[23] Eaton et al,[24] and Shapira Y.[25]
†Aladjidi et al.[26]
‡Moulis et al.[27]
§Danner et al.[28]
‖Peneau et al[29] and Gower-Rousseau et al.[30]

TABLE IV. Frequency of multiple occurrences of autoimmune/inflammatory manifestations in patients with PIDs

No. of manifestations per patient		Percentage of patients
0	1612	73.8
1	389	17.8
2	113	5.2
3	44	2.0
4	20	.9
5	4	.2
6	1	

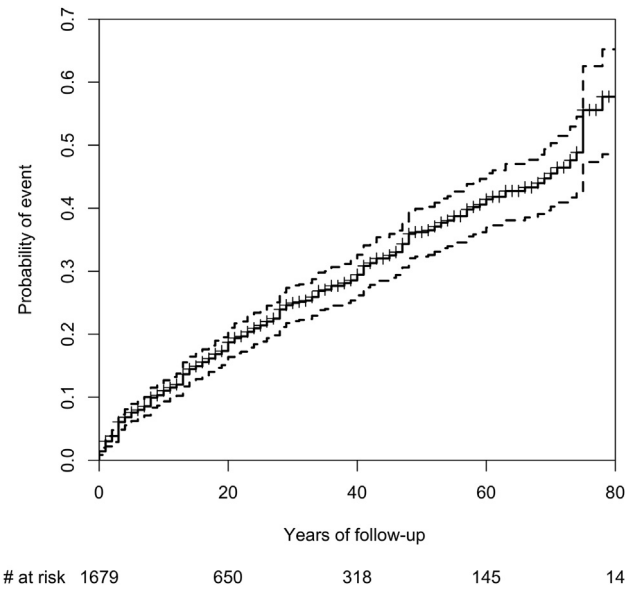

FIG 1. Cumulative incidence of autoimmune/inflammatory manifestations in patients with PIDs as a function of age. Data are from 1678 patients for whom age at onset of first manifestation was recorded. *Dotted lines* indicate ± 2 SDs.

Our results confirmed literature reports[16,17] in which CVID was frequently associated with autoimmunity/inflammation, including granulomas. Although the prominence of autoimmunity in patients with T-cell immunodeficiencies had been suspected, it was confirmed by our data. In contrast, we were somewhat surprised to observe that autoimmune/inflammatory manifestations are rather common complications of all types of PIDs, including innate immune deficiencies. In the latter group inflammatory lesions and, notably, inflammatory bowel disease were particularly frequent. It is also important to note that the risk of onset of autoimmunity persists throughout the patient's life; however, this should be put in perspective with the fact that a causal factor is continuously present. In contrast to the situation in the general population, no real sex bias was observed in patients with PIDs; this finding suggests that the known sex-associated risk factors (×1.7[22]) are not exacerbated by PIDs. Furthermore, the occurrence of other noninfectious complications of PIDs, such as allergy and cancer, is associated with autoimmunity/inflammation. At this time, we cannot say whether allergy and cancer should be considered risk factors or rather common consequences of the underlying PID. However, we suspect that pre-existing allergy might have a role based on the adjusted Cox model analysis.

The influence of infections on autoimmunity/inflammation has not been characterized and thus warrants specific attention in prospective studies. It is possible that persistent infection in a patient with a PID might trigger autoimmunity and accentuate inflammation, as suggested by the recent report in which persistent rubella vaccine virus was found in granulomas in patients with several PIDs.[31]

Lastly, our results show that autoimmunity worsens the prognosis for patients with a PID. The latter finding highlights the need for careful examination of the efficacy/toxicity balance of both biologic and nonbiologic immunosuppressive treatment for autoimmunity in the context of PIDs.

TABLE V. Univariate analysis of risk factors for the occurrence of autoimmunity, inflammation, or both

		Autoimmunity/ inflammation		
	No.	No.	Percentage	*P* value
All patients	2183	571	26.2	
Male sex	1255	320	25.5	NS
PID diagnosis				<.001
B-cell PIDs	993	253	25.5	
CVID	408	156	38.3	
Non-CVID	585	97	16.6	
T-cell PIDs	845	232	27.5	<.001
Severe combined immunodeficiency (SCID)	160	11	6.9	
Combined immunodeficiency (CID)	424	132	31.1	
Others	261	89	31.7	
Innate	323	83	25.6	NS
Unclassified	21	4	19.0	
Allergy	395	123	31.1	.0009
Cancer	148	55	37.2	.002

NS, Not significant.

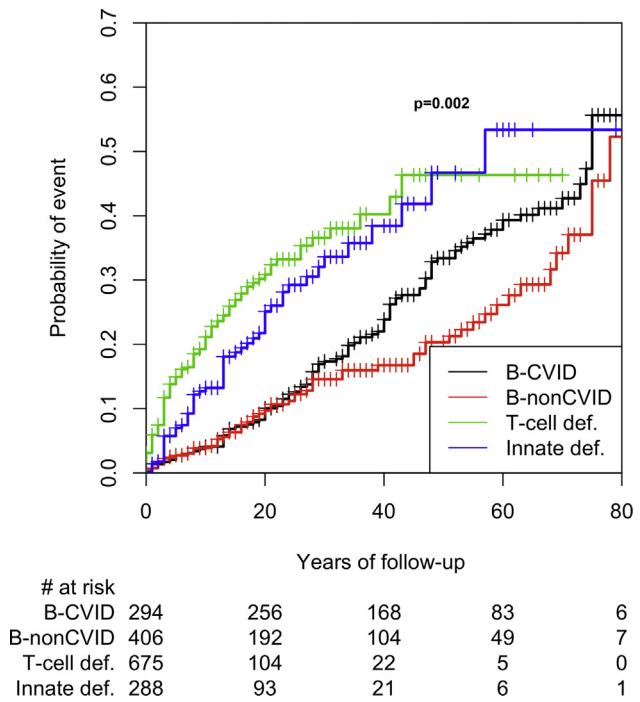

FIG 2. Cumulative incidence of autoimmunity/inflammatory manifestations in patients with PIDs as a function of the PID disease group.

Many researchers have discussed the various mechanisms by which autoimmunity/inflammation can be triggered in the context of PIDs.[11-13,31,32] These mechanisms include (1) exacerbated production of type I interferon, (2) IL-1 production, (3) defective negative selection of self-reactive T and B cells with high affinity, (4) defective editing of the B-cell receptor in the periphery, (5) defective peripheral (self)-antigen–induced cell death, (6) gain of function of B- or T-cell activation/effector molecules, (7) defective regulatory T cells, (8) homeostatic expansion of self-reactive T lymphocytes, (9) an intrinsic defect in cis regulatory molecules, and (10) defective clearance of immune complexes and apoptotic cell bodies. *A la carte* combinations of these factors in patients with various PIDs can predispose patients to autoimmunity and inflammation. It is beyond the scope of this study to discuss in detail the involvement of these mechanisms, when recognized, in patients with the many PIDs associated with autoimmunity.

In conclusion, the present study both provides valuable information and raises further questions on the occurrence of autoimmune/inflammatory diseases in patients with PIDs. For scientific and medical reasons, a detailed international analysis of these complications, such as a prospective analysis of a large cohort of patients with PIDs, should now be organized.

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TABLE VI. Adjusted Cox model of variables associated with autoimmunity/inflammation*

Risk factor	Hazard ratio (95% CI)	*P* value
PID category		
CVID	1	—
Other (non-CVID) B-cell deficiencies	0.80 (0.47-1.38)	.42
T-cell deficiencies	**3.17 (1.92-5.24)**	**<.001**
Innate immunity deficiencies	**3.16 (1.61-6.20)**	**<.001**
Allergy	**7.44 (4.92-11.26)**	**<.001**
Malignancy	0.70 (0.35-1.38)	.30

Significant hazard ratios are in boldface.
*For patients with no missing data for the model's variables.

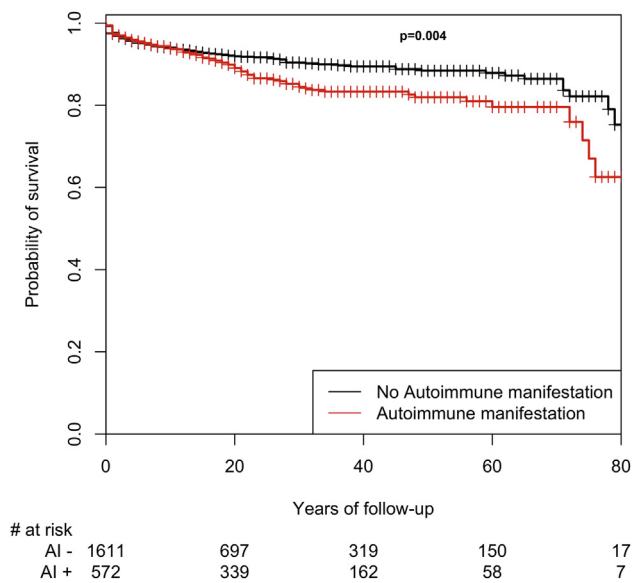

FIG 3. Probability of survival of patients with PIDs as a function of the occurrence of autoimmune/inflammatory manifestations.

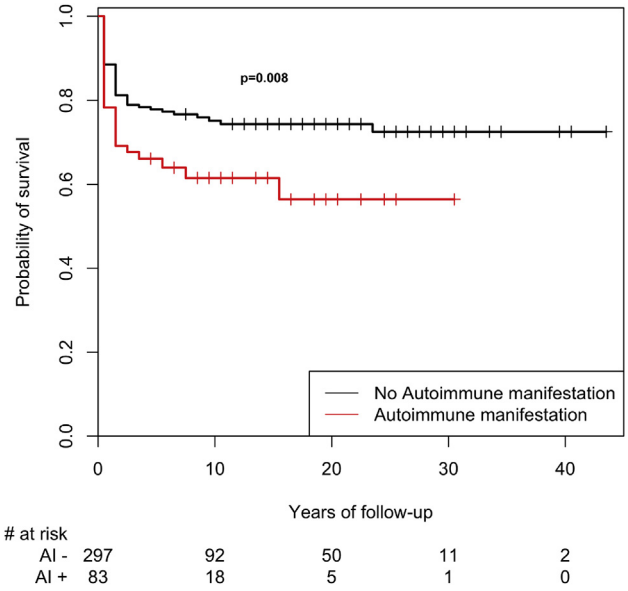

FIG 4. Probability of survival of patients with PIDs after HSCT, according to the presence or absence of pre-existing autoimmunity/inflammation.

REFERENCES

1. Matamoros Flori N, Mila Llambi J, Espanol Boren T, Raga Borja S, Fontan Casariego G. Primary immunodeficiency syndrome in Spain: first report of the National Registry in Children and Adults. J Clin Immunol 1997;17:333-9.
2. Kirkpatrick P, Riminton S. Primary immunodeficiency diseases in Australia and New Zealand. J Clin Immunol 2007;27:517-24.
3. CEREDIH: the French PID study group. The French National Registry of Primary Immunodeficiency Disease. Clin Immunol 2010;135:264-72.
4. Edgar JD, Buckland M, Guzman D, Conlon NP, Knerr V, Bangs C, et al. The United Kingdom Primary Immune Deficiency (UKPID) Registry: report of the first 4 years' activity 2008-2012. Clin Exp Immunol 2014;175:68-78.
5. Jonkman-Berk BM, van den Berg JM, Ten Berge IJ, Bredius RG, Driessen GJ, Dalm VA, et al. Primary immunodeficiencies in the Netherlands: national patient data demonstrate the increased risk of malignancy. Clin Immunol 2015;156:154-62.
6. Marschall K, Hoernes M, Bitzenhofer-Gruber M, Jandus P, Duppenthaler A, Wuillemin WA, et al. The Swiss National Registry for Primary Immunodeficiencies: report on the first 6 years' activity from 2008 to 2014. Clin Exp Immunol 2015;182:45-50.
7. Picard C, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, et al. Primary Immunodeficiency Diseases: an update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. J Clin Immunol 2015;35:696-726.
8. Suarez F, Mahlaoui N, Canioni D, Andriamanga C, Dubois d'Enghien C, Brousse N, et al. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French national registry of primary immune deficiencies. J Clin Oncol 2015;33:202-8.
9. Shapiro RS. Malignancies in the setting of primary immunodeficiency: implications for hematologists/oncologists. Am J Hematol 2011;86:48-55.
10. Tuano KS, Orange JS, Sullivan K, Cunningham-Rundles C, Bonilla FA, Davis CM. Food allergy in patients with primary immunodeficiency diseases: prevalence within the US Immunodeficiency Network (USIDNET). J Allergy Clin Immunol 2015;135:273-5.
11. Saifi M, Wysocki CA. Autoimmune disease in primary immunodeficiency: at the crossroads of anti-infective immunity and self-tolerance. Immunol Allergy Clin North Am 2015;35:731-52.
12. Grimbacher B, Warnatz K, Yong PF, Korganow AS, Peter HH. The crossroads of autoimmunity and immunodeficiency: Lessons from polygenic traits and monogenic defects. J Allergy Clin Immunol 2016;137:3-17.
13. de Jesus AA, Canna SW, Liu Y, Goldbach-Mansky R. Molecular mechanisms in genetically defined autoinflammatory diseases: disorders of amplified danger signaling. Annu Rev Immunol 2015;33:823-74.
14. Kolhatkar NS, Brahmandam A, Thouvenel CD, Becker-Herman S, Jacobs HM, Schwartz MA, et al. Altered BCR and TLR signals promote enhanced positive selection of autoreactive transitional B cells in Wiskott-Aldrich syndrome. J Exp Med 2015;212:1663-77.
15. Magnani A, Brosselin P, Beaute J, de Vergnes N, Mouy R, Debre M, et al. Inflammatory manifestations in a single-center cohort of patients with chronic granulomatous disease. J Allergy Clin Immunol 2014;134:655-62.e8.
16. Warnatz K, Voll RE. Pathogenesis of autoimmunity in common variable immunodeficiency. Front Immunol 2012;3:210.
17. Gathmann B, Mahlaoui N, Ceredih, Gerard L, Oksenhendler E, Warnatz K, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol 2014;134:116-26.
18. R Core Team. A language and environment for statistical computing. Vienna (Austria): R Foundation for Statistical Computing; 2015. Availble at: https://R-project.org.
19. Hayter SM, Cook MC. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. Autoimmun Rev 2012;11:754-65.
20. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. Autoimmun Rev 2003;2:119-25.
21. Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. J Autoimmun 2009;33:197-207.
22. Ramos-Casals M, Brito-Zeron P, Kostov B, Siso-Almirall A, Bosch X, Buss D, et al. Google-driven search for big data in autoimmune geoepidemiology: analysis of 394,827 patients with systemic autoimmune diseases. Autoimmun Rev 2015;14:670-9.
23. Ji J, Sundquist J, Sundquist K. Gender-specific incidence of autoimmune diseases from national registers. J Autoimmun 2016;69:102-6.
24. Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. J Autoimmun 2007;29:1-9.
25. Shapira Y, Agmon-Levin N, Shoenfeld Y. Defining and analyzing geoepidemiology and human autoimmunity. J Autoimmun 2010;34:J168-77.
26. Aladjidi N, Leverger G, Leblanc T, Picat MQ, Michel G, Bertrand Y, et al. New insights into childhood autoimmune hemolytic anemia: a French national observational study of 265 children. Haematologica 2011;96:655-63.
27. Moulis G, Palmaro A, Montastruc JL, Godeau B, Lapeyre-Mestre M, Sailler L. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. Blood 2014;124:3308-15.
28. Danner S, Sordet C, Terzic J, Donato L, Velten M, Fischbach M, et al. Epidemiology of juvenile idiopathic arthritis in Alsace, France. J Rheumatol 2006;33:1377-81.
29. Peneau A, Savoye G, Turck D, Dauchet L, Fumery M, Salleron J, et al. Mortality and cancer in pediatric-onset inflammatory bowel disease: a population-based study. Am J Gastroenterol 2013;108:1647-53.
30. Gower-Rousseau C, Vasseur F, Fumery M, Savoye G, Salleron J, Dauchet L, et al. Epidemiology of inflammatory bowel diseases: new insights from a French population-based registry (EPIMAD). Dig Liver Dis 2013;45:89-94.
31. Bodemer C, Sauvage V, Mahlaoui N, Cheval J, Couderc T, Leclerc-Mercier S, et al. Live rubella virus vaccine long-term persistence as an antigenic trigger of cutaneous granulomas in patients with primary immunodeficiency. Clin Microbiol Infect 2014;20:O656-63.
32. Notarangelo LD. Functional T cell immunodeficiencies (with T cells present). Annu Rev Immunol 2013;31:195-225.

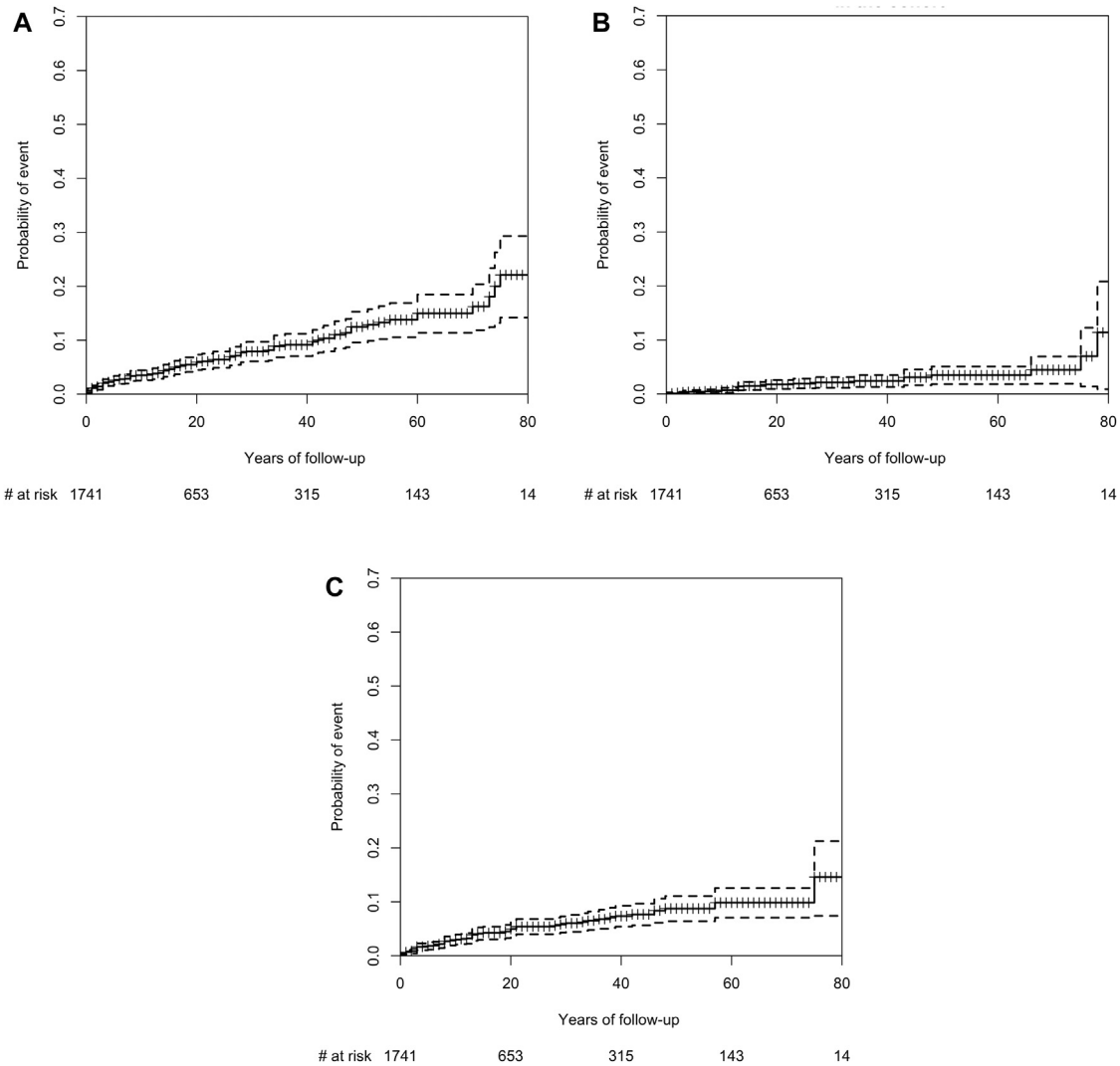

FIG E1. Cumulative incidence of cytopenia, rheumatologic disorders, and autoimmune gastrointestinal manifestations as a function of age. **A,** Autoimmune cytopenia. **B,** Rheumatologic disorders. **C,** Gastrointestinal disorders.

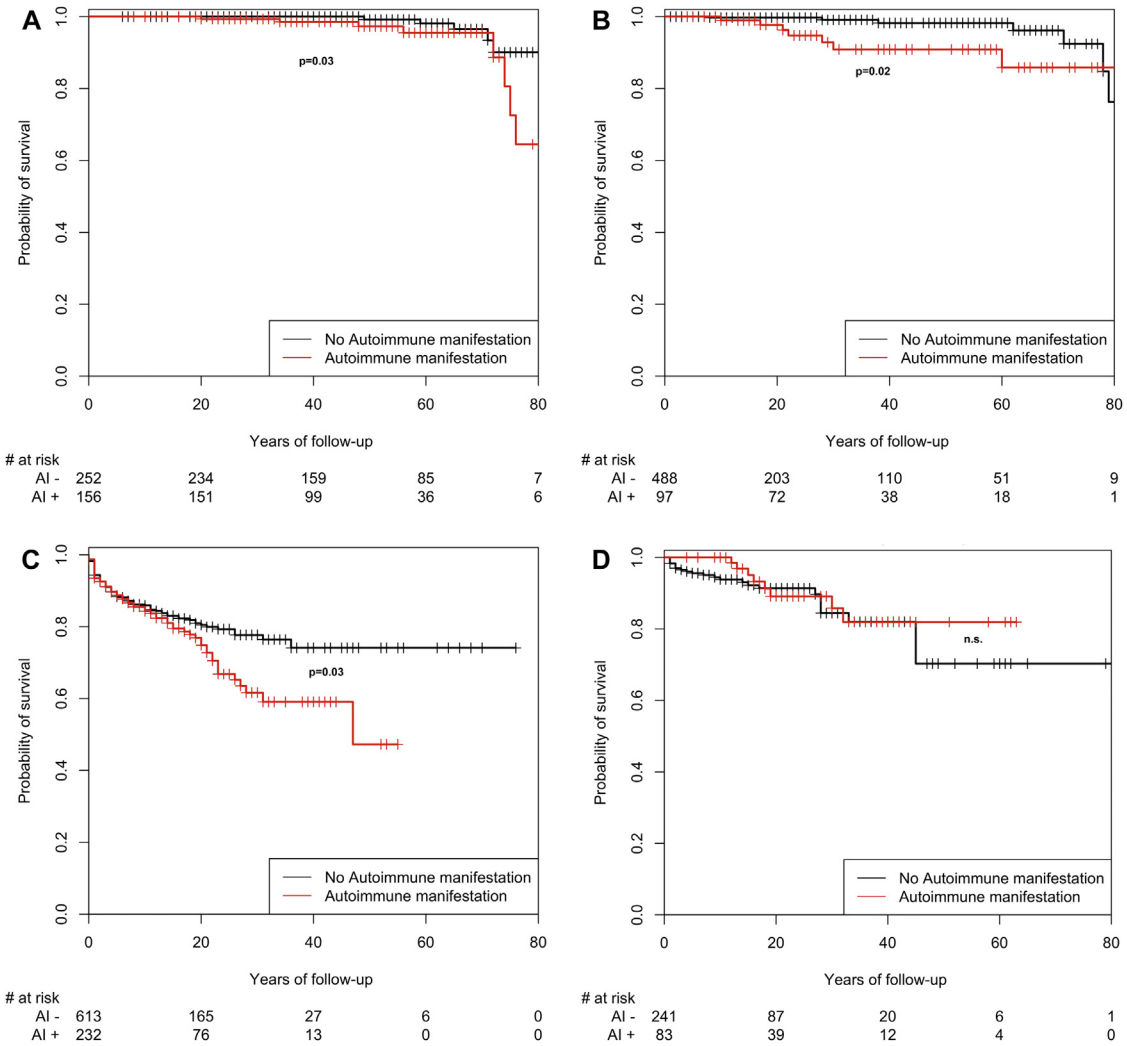

FIG E2. Survival of PID patients with CVID **(A)**, other B-cell PIDs **(B)**, T-cell PIDs **(C)**, and innate PIDs **(D)** as a function of the occurrence of autoimmunity/inflammation.

TABLE E1. List of autoimmune and inflammatory manifestations reported in patients with PIDs (International Classification of Diseases, 10th Revision)

Cytopenia
Idiopathic thrombocytopenic purpura
Other autoimmune hemolytic anemias
Agranulocytosis
Idiopathic aplastic anemia
Acquired pure red cell aplasia (erythroblastopenia)
Rheumatologic disorders
Arthritis, unspecified
Polyarthritis, unspecified
Systemic lupus erythematosus, unspecified
Lupus erythematosus
Rheumatoid arthritis, unspecified
Other rheumatoid arthritis
Raynaud syndrome
Ankylosing spondylitis
Pain in joint
Sicca syndrome (Sjögren syndrome)
Endocrine disorders
Autoimmune thyroiditis
Insulin-dependent diabetes mellitus
Hypoparathyroidism
Skin
Psoriasis
Vasculitis limited to skin, unspecified
Vitiligo
Alopecia areata
Pemphigus, unspecified
Allergic purpura
Dermatopolymyositis
Granulomatous disorders of skin and subcutaneous tissue
Granuloma annulare
Panniculitis, unspecified
Gastrointestinal disorders
Autoimmune hepatitis
Celiac disease
Vitamin B12 deficiency anemia caused by intrinsic factor deficiency
Primary biliary cirrhosis
Crohn disease, unspecified
Ulcerative (chronic) pancolitis
Crohn disease (regional enteritis)
Crohn disease of large intestine
Other specified diseases of intestine
Other specified noninfective gastroenteritis and colitis
Gastroenteritis and colitis of unspecified origin
Chronic atrophic gastritis
Other gastritis
Adult hypertrophic pyloric stenosis
Recurrent oral aphthae
Stomatitis and related lesions
Ulcer of anus and rectum
Anal fistula
Granulomatous hepatitis, not elsewhere classified
Liver disorders in other diseases classified elsewhere
Kidney
Glomerular disorders in blood diseases and disorders involving the immune mechanism
Recurrent and persistent hematuria: Other
Nephrotic syndrome
Unspecified nephritic syndrome: Diffuse crescentic glomerulonephritis

(Continued)

TABLE E1. *(Continued)*

Neurologic disorders
Myasthenia gravis
Intracranial and intraspinal and granuloma in diseases classified elsewhere
Progressive multifocal leukoencephalopathy
Encephalitis, myelitis, and encephalomyelitis, unspecified
Lung
Other interstitial pulmonary diseases
Other interstitial pulmonary diseases with fibrosis
Sarcoidosis, unspecified
Eyes
Focal chorioretinal inflammation
Other endophthalmitis
Keratitis
Episcleritis
Vasculitis
Cerebral arteritis, not elsewhere classified
Arteritis, unspecified
Other giant cell arteritis
Systemic
Systemic inflammatory response syndrome of noninfectious origin without organ failure
Urologic disorders
Inflammatory disorders of seminal vesicle
Other
Other osteomyelitis
Assessment of infection: Independent skin manifestation among patients with the different PIDs

Skin manifestations	Frequency
Psoriasis	26
Vasculitis limited to skin, unspecified	24
Granulomatous disorders of skin and subcutaneous tissue	21
Vitiligo	16
Alopecia areata	13
Pemphigus, unspecified	1
Dermatitis, unspecified	1
Granuloma annulare	1
Panniculitis, unspecified	1

TABLE E2. Comparison of the demographic characteristics of the study population and the overall registry population

	Overall registry population		Study population		
	No. of patients	**Percent**	**No. of patients**	**Percent**	***P* value**
Total	5952	100	2183	100	
Male sex	3378	56.8	1264	57.9	.37
Age (y), median (Q1-Q3)	20 (10-41)		20 (9-38)		.053
Main PID categories					
Adaptive immunodeficiencies					
B-cell CVID	1171	19.7	408	18.7	.34
Other (non-CVID) B-cell PIDs	1530	25.7	585	26.8	.33
T-cell severe combined immunodeficiency	368	6.2	160	7.3	.07
T-cell combined immunodeficiency	931	15.6	334	15.3	.73
Other T-cell PIDs	781	13.1	351	16.1	**<.01**
Innate PIDs	1123	18.9	324	14.8	**<.01**
Unclassified PIDs	48	0.8	21	1.0	.59

TABLE E3. Number of patients with autoimmune or inflammatory manifestations, by PID category

PID category	No. of manifestations							
	0	1	2	3	4	5	6	Total
Agammaglobulinemia	88	7	3	0	0	0	0	98
Asplenia syndrome (Ivemark syndrome)	1	0	0	0	0	0	0	1
Ataxia telangiectasia (ATM)	55	12	3	0	0	0	0	70
Atypical severe combined immunodeficiency	8	4	1	0	0	0	0	13
Autoimmune lymphoproliferative syndrome (ALPS)	23	25	5	3	0	0	0	56
Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED)	0	4	1	1	1	1	1	9
Barth syndrome	3	0	0	0	0	0	0	3
Bloom syndrome (RECQ2)	1	1	0	0	0	0	0	2
CARD9 deficiency	1	0	0	0	0	0	0	1
Cartilage-hair hypoplasia	7	1	1	0	0	0	0	9
CCAAT/enhancer binding protein epsilon deficiency (CEBPE)	1	0	0	0	0	0	0	1
CD8 deficiency	2	1	0	0	0	0	0	3
Chediak-Higashi syndrome	11	0	0	0	0	0	0	11
Chronic granulomatous disease (CGD)	47	32	12	3	2	0	0	96
Chronic mucocutaneous candidiasis (CMC)	14	5	0	0	0	0	0	19
Clericuzio-type poikiloderma with neutropenia syndrome	0	1	0	0	0	0	0	1
COHEN syndrome	0	0	1	0	0	0	0	1
Combined immunodeficiency	75	20	14	6	0	1	0	116
CVID	252	110	28	14	4	0	0	408
Complement component 2 deficiency	7	2	0	1	0	0	0	10
Complement component 4 deficiency	1	2	1	1	0	0	0	5
Complement component 5 deficiency	4	0	0	0	0	0	0	4
Complement component 6 deficiency	5	0	0	0	0	0	0	5
Complement component 7 deficiency	1	1	0	0	0	0	0	2
Complement component 9 deficiency	1	0	0	0	0	0	0	1
Congenital neutropenia	42	7	1	0	0	0	0	50
Congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD)	2	0	0	0	0	0	0	2
Class-switch recombination defects and hyper-IgM (HIGM) syndromes	29	6	1	0	0	0	0	36
Cyclic neutropenia	12	1	0	0	1	0	0	14
Defects of Toll-like receptor/nuclear factor κB signaling	2	0	0	0	0	0	0	2
Defects with susceptibility to mycobacterial infection (MSMD)	13	1	1	0	0	0	0	15
Deficiency of specific IgG (specific antibody deficiency [SPAD])	6	0	0	1	0	0	0	7
DiGeorge syndrome (DGS)	24	9	1	4	0	0	0	38
Dyskeratosis congenita	4	0	0	0	0	0	0	4
Early-onset inflammatory bowel disease	3	1	0	0	0	0	0	4
Facial dysmorphism, immunodeficiency, livedo, and short stature (FILS)	10	0	0	0	0	0	0	10
Factor I deficiency	3	0	0	0	0	0	0	3
Familial hemophagocytic lymphohistiocytosis (FHLH) syndromes	47	0	0	1	0	0	0	48
FOXP3 deficiency (immune dysfunction, polyendocrinopathy, enteropathy, X-linked syndrome)	0	9	2	3	3	1	0	18
Glycogen storage disease type 1b (GS1b)	2	0	0	0	0	0	0	2
Griscelli syndrome, type 2	6	1	0	0	0	0	0	7
Herpetic encephalitis	6	0	0	0	0	0	0	6
HLA class II deficiency	19	6	0	0	0	0	0	25
Hoyeraal-Hreidarsson syndrome	2	1	0	0	0	0	0	3
Hyper-IgE syndrome	53	2	0	0	0	0	0	55
IgA with IgG subclass deficiency	4	5	1	1	0	0	0	11
Immunodeficiencies with multiple intestinal atresias	1	0	0	0	0	0	0	1
Immunodeficiency centromeric instability facial anomalies syndrome (ICF)	4	1	0	0	1	0	0	6
Infancy onset STING-associated vasculopathy	1	0	1	0	0	0	0	2
IL-2 receptor α deficiency (CD25 [immune dysfunction, polyendocrinopathy, enteropathy, X-linked phenotype])	0	0	0	0	1	0	0	1
Immune dysfunction, polyendocrinopathy, enteropathy, X-linked syndrome–like disease	0	0	1	0	0	0	0	1
Isolated congenital asplenia	25	0	0	0	0	0	0	25
Isolated IgG subclass deficiency	207	22	5	0	0	0	0	234
Leukocyte adhesion deficiency	6	0	0	0	0	0	0	6
Monocytopenia and mycobacterial infection	1	1	1	0	0	0	0	3
Omenn syndrome	22	2	0	0	0	0	0	24
Other autoinflammatory diseases with known genetic defect	0	3	0	0	0	0	0	3
Properdin P factor complement deficiency (PFC)	2	0	0	0	0	0	0	2
Pulmonary alveolar proteinosis	1	0	0	0	0	0	0	1
Ras-associated lymphoproliferative disease (RALD)	0	1	0	0	0	0	0	1

(Continued)

TABLE E3. *(Continued)*

PID category	No. of manifestations							
	0	1	2	3	4	5	6	Total
Schimke disease	2	0	0	0	0	0	0	2
Seckel syndrome	0	0	0	0	0	0	0	0
Selective CD4 cell deficiency	5	0	0	0	0	0	0	5
Selective IgA deficiency (symptomatic)	39	8	0	0	0	0	0	47
Selective IgM deficiency	4	0	0	0	0	0	0	4
Severe combined immunodeficiency (SCID)	126	8	1	0	0	0	0	135
Shwachman-Diamond syndrome	29	2	0	0	0	0	0	31
Steinert myotonic dystrophy	0	2	0	0	0	0	0	2
Thymoma with immunodeficiency	11	5	1	0	0	0	0	17
Trichohepatoenteric syndrome	1	0	0	0	0	0	0	1
Unclassified antibody deficiency	122	20	7	3	3	0	0	155
Unclassified complement deficiencies	1	0	0	0	0	0	0	1
Unclassified defects in innate immunity	4	2	0	0	0	0	0	6
Unclassified disorders of immune dysregulation	2	3	2	1	2	1	0	11
Unclassified immunodeficiencies	17	3	0	0	0	0	0	20
Unclassified phagocytic disorders	2	1	0	0	0	0	0	3
Unclassified syndromic immunodeficiencies	0	0	1	0	0	0	0	1
Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM)	2	0	0	0	0	0	0	2
Warts, immunodeficiency, lymphedema, dysplasia (WILD) syndrome	1	0	0	0	0	0	0	1
Winged-helix nude deficiency (FOXN1)	1	0	0	0	0	0	0	1
Wiskott-Aldrich syndrome (WAS)	50	26	11	1	2	0	0	90
X-linked lymphoproliferative syndrome (XLP)	22	5	5	0	0	0	0	32
Unclassified	1	0	0	0	0	0	0	1

TABLE E4. Distribution of major autoimmune/inflammatory manifestations among the main groups of PIDs

	Overall no. of patients in the study cohort	Cytopenia (%)	Gastrointestinal manifestations (%)	Rheumatologic manifestations (%)
1. Adaptive immunity, B-cell deficiencies, CVID	408	16.7	10.0	5.4
2. Adaptive immunity, B-cell deficiencies, non-CVID	585	3.9	4.4	4.3
3. Adaptive immunity, T-cell deficiencies, severe combined immunodeficiency	160	3.1	1.3	0.6
4. Adaptive immunity, T-cell deficiencies, combined immunodeficiency	424	14.6	5.9	6.6
5. Adaptive immunity, other T-cell deficiencies	261	19.2	14.6	3.1
6. Innate immunity deficiencies	324	2.8	15.4	4.9
7. Unclassified PID	21	4.8	9.5	0.0
Detailed description of PIDs				
Agammaglobulinemia	98	2.0	6.1	1.0
Autoimmune lymphoproliferative syndrome	56	53.6	5.4	1.8
Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy	9	22.0	44.4	11.1
Asplenia	26	0.0	0.0	0.0
Ataxia telangiectasia and other DNA-breakage disorders	78	3.8	5.1	2.6
Autoimmune and immune dysregulation	19	36.8	26.3	5.3
Chronic granulomatous disease (CGD)	96	1.0	44.8	2.1
CHS	11	0.0	0.0	0.0
Combined immunodeficiency	256	13.3	7.8	5.9
Complement	33	3.0	0.0	21.2
CSR defects and hyper-IgM syndromes	10	20.0	0.0	10.0
CVID	408	16.7	9.6	5.4
Familial hemophagocytic lymphohistiocytosis	48	2.1	2.1	0.0
GS2	7	14.3	0.0	0.0
Hyper-IgE syndrome	55	0.0	1.8	0.0
Herpetic encephalitis	7	0.0	0.0	0.0
Hypogammaglobulinemia	477	4.0	3.8	4.8
Immune dysfunction, polyendocrinopathy, enteropathy, X-linked	24	33.3	66.7	4.2
Leukocyte adhesion deficiency	6	0.0	0.0	0.0
Monocytopenia and mycobacterial infection	4	25.0	0.0	0.0
Defects with susceptibility to mycobacterial infection	15	0.0	0.0	6.7
Other Innate	24	0.0	8.3	0.0
Other phagocytic and innate immunity disorders	9	0.0	11.1	0.0
Severe combined immunodeficiency	160	3.1	1.3	0.6
Severe congenital neutropenia	104	5.8	3.8	5.8
Unclassified	21	4.8	9.5	0.0
Wiskott-Aldrich syndrome	90	27.8	1.1	12.2
X-linked lymphoproliferative syndrome	32	3.1	18.8	12.5

TABLE E5. List of allergies encountered in patients with PIDs

Allergic respiratory manifestations
Asthma
Respiratory disorder, unspecified
Allergic rhinitis, unspecified
Allergic rhinitis caused by pollen
Allergic skin manifestations
Dermatitis, unspecified
Other atopic dermatitis
Allergic digestive manifestations
Allergic and dietetic gastroenteritis and colitis
Allergic urticaria
Malabsorption caused by intolerance, not elsewhere classified
Other adverse food reactions, not elsewhere classified
Other allergic manifestations
Allergy, unspecified
Anaphylactic shock, unspecified
Conjunctivitis
Unspecified adverse effect of drug or medicament
Desensitization to allergens

Groupings of detailed allergic manifestations according to localization, affected organ, or system (International Classification of Diseases, 10th Revision, labels) are shown in boldface.