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Autoimmune Cytopenias and Associated Conditions in CVID: a Report From the USIDNET Registry

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Abstract

Purpose—Autoimmune cytopenia is frequently a presenting manifestation of common variable immune deficiency (CVID). Studies characterizing the CVID phenotype associated with autoimmune cytopenias have mostly been limited to large referral centers. Here, we report prevalence of autoimmune cytopenias in CVID from the USIDNET Registry and compare the demographics and clinical features of patients with and without this complication.

Methods—Investigators obtained demographic, laboratory, and clinical data on CVID patients within the USIDNET Registry. Patients were considered to have autoimmune cytopenia if they had a diagnosis of hemolytic anemia, immune thrombocytopenia (ITP), or autoimmune neutropenia. Baseline characteristics and associated complications of those with autoimmune cytopenia (+AC) and those without (–AC) were compared.

Results—Of 990 CVID patients included in the analysis, 10.2% ($N = 101$) had a diagnosis consistent with autoimmune cytopenia: ITP was diagnosed in 7.4% ($N = 73$), hemolytic anemia in 4.5% ($N = 45$), and autoimmune neutropenia in 1% ($N = 10$). Age at diagnosis, gender, and baseline Ig values did not differ between the +AC and –AC groups. The +AC group was significantly more likely to have one or more other CVID-associated non-infectious complications (OR = 2.9; 95%-CI: 1.9–4.6, $P < 0.001$), including lymphoproliferation, granulomatous disease, lymphomas, hepatic disease, interstitial lung diseases, enteropathy, and organ-specific autoimmunity.

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Authors Contributions Dr. Feuille assisted in study design, conducted statistical analysis on survey responses, drafted the initial manuscript, and approved the final manuscript as submitted.

Dr. Anooshiravani assisted with study design, analysis and interpretation of data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr. Fuleihan assisted with study design, analysis and interpretation of data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr. Cunningham-Rundles conceptualized the study, assisted in analysis and interpretation of data, drafted the initial manuscript, and approved the final manuscript as submitted.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

Conclusions—Autoimmune cytopenias are a common manifestation in CVID and are likely to be associated with other non-infectious CVID-related conditions. In light of prior studies showing increased morbidity and mortality in CVID patients with such complications, a diagnosis of autoimmune cytopenia may have prognostic significance in CVID.

Keywords

Common variable immunodeficiency; autoimmunity; immune thrombocytopenia; Evans syndrome; neutropenia; hemolytic anemia

Introduction

Common variable immune deficiency (CVID) is a primary immunodeficiency characterized by decreased or absent antibody production and impaired humoral immune function [1, 2]. With an incidence of 1:50,000 to 25,000, it is the most common primary immunodeficiency syndrome leading to medical intervention. In addition to frequent infections, subjects with CVID may also develop non-infectious complications, including interstitial lung and/or gastrointestinal inflammatory disease, hematologic or organ-specific autoimmunity, lymphoproliferation, and in some cases, lymphoma [3–6]. Partly, as a consequence of its diverse manifestations and rather late onset, diagnostic delays in CVID are common, with a median time to diagnosis of 4 to 6 years [6, 7]. With the advent of immunoglobulin (Ig) therapy, non-infectious complications have become important causes of death and disability in CVID. Increased morbidity and/or mortality have been particularly associated with enteropathy, chronic lung disease, hepatic disease, lymphoma, lymphoproliferation, and/or auto-immunity [3, 4].

Autoimmune cytopenias are reported among CVID patients with a prevalence between 11 to 18% [3, 4, 6, 8]. With cytopenias being a common early manifestation of this immune deficiency [8–10], an understanding of CVID manifestations associated with autoimmune cytopenias may prove useful in predicting prognosis and monitoring for additional complications. Other studies have addressed the possible correlation between cytopenias and complications of CVID in referral centers, including interstitial lung disease [11, 12] and nodular regenerative hyperplasia (NRH) of the liver [13], and peripheral B cell phenotypes [8]. In this study, we examine the prevalence of cytopenias among 990 patients with CVID who were enrolled into the USIDNET registry from 50 medical centers and compare the baseline characteristics and associated complications among patients with and without autoimmune cytopenias.

Methods

The USIDNET Registry, funded by the NIH in a cooperative grant to the Immune Deficiency Foundation, provides and maintains clinical and laboratory data on patients with primary immune deficiency diseases in the USA and Canada (USIDNET.org). After consent, data are entered by enrolling institutions or by patients via a link allowing them to provide medical records. In both cases, the diagnosis and entered data are confirmed by their physician. Investigators may query the Registry and obtain de-identified patient data for research or other analysis.

For the current study, a query was submitted to the USIDNET Registry requesting demographics, age at diagnosis, conditions, and Ig levels for patients with a diagnosis of CVID. Subjects with thymoma ($N=10$) were excluded. Patients were included in the analysis if they had at least one IgA and/or IgM value less than two standard deviations below standard laboratory mean for age (for adults: IgA < 70 mg/dL; IgM < 40 mg/dL). We did not exclude patients with IgG levels within 2 standard deviations of the laboratory mean, as baseline IgG values were not always available and patients may have been on Ig replacement at the time of enrollment. Where multiple IgG values were entered, the lowest was used here. For data on cytopenias, all data fields for anemia, thrombocytopenia, and neutropenia were examined. Only the following diagnoses (or variations of these) were classified as autoimmune cytopenias: immune thrombocytopenia (ITP, idiopathic thrombocytopenic purpura), hemolytic anemia (autoimmune hemolytic anemia, AIHA, coombs + anemia, immune anemia), autoimmune neutropenia, or Evan's syndrome. Demographics, age at diagnosis, Ig values, autoimmune conditions, and other CVID-associated complications of subjects with (+AC) or without autoimmune cytopenia (-AC) were compared. Specifically, prevalences of pulmonary, gastrointestinal, hepatic, lymphatic, granulomatous, and hematologic complications were compared among CVID patients with and without autoimmune cytopenia. Table 3 details included diagnoses under each category. Additionally, prevalence of systemic autoimmunity and organ-specific autoimmunity (which included diagnoses consistent with integumentary, endocrine, and ocular autoimmunity as well as autoimmune enteropathy and autoimmune hepatitis) were compared among CVID patients with and without autoimmune cytopenia. Table 4 details included diagnoses. Of note, sarcoidosis was excluded from systemic autoimmunity, due to concerns that granulomatous complications of CVID are often mischaracterized as sarcoidosis. As with autoimmune cytopenias, diagnoses are presented as entered by contributors to the USIDNET Registry; supporting data for each diagnosis was not elicited from contributors.

Statistical Analysis

The baseline characteristics of subjects with and without autoimmune cytopenia(s) were compared using "N-1" Chi-squared test for categorical variables (MedCalc® Software © 2017), and using two-tailed, heteroscedastic *t* test for continuous variables (Microsoft® Excel for Mac © 2017). Prevalence of autoimmune conditions and other non-infectious CVID-associated complications among subjects with and without autoimmune cytopenia were then compared using odds ratio with mid-P calculation (MedCalc® Software © 2017).

Results

There were 1435 patients in the USIDNET Registry with a diagnosis of CVID in February 2017. These data were entered by 173 contributors from 50 institutions, with a median of 6 (IQR 1 to 23) patients entered per institution. Of these, 990 had at least one IgM or IgA value 2 standard deviations below standard laboratory mean, compatible with the CVID diagnosis; these subjects are included in these analyses.

Autoimmune Cytopenias

Of the 990 CVID patients, 10.2% ($N = 101$) had a diagnosis consistent with autoimmune cytopenia (Table 1). ITP was the most commonly reported autoimmune cytopenia ($n = 73$; 7.4%). Hemolytic anemia (including AIHA) was reported in 4.5% ($N = 45$), and autoimmune neutropenia in 1% ($N = 10$). In addition, 38 (3.8%) had a cytopenias affecting at least 2 cell lines and 16 (1.6%) were labeled with a diagnosis of Evan's syndrome.

Comparison of CVID Patients With and Without Autoimmune Cytopenia

Gender, race, ethnicity, age, and IgG, IgA, or IgM levels were not significantly different for subjects with or without an autoimmune cytopenia (Table 2). While a somewhat greater number of the +AC group was male (51.5%), compared to the -AC group (45.6%), this was not statistically significant ($P = 0.26$). The majority of both groups were Caucasian and non-Hispanic. The median age of CVID symptom onset was 16 years for both groups. Those in +AC group were somewhat younger at most recent data entry (median age 30 years) compared to those in -AC group (median age 36 years), but this was not statistically significant ($P = 0.124$). Median IgG and IgA values appeared lower and median IgM values higher among +AC patients, compared to -AC patients, but differences were not statistically significant ($P = 0.974$, $P = 0.163$, and $P = 0.203$, respectively).

Non-infectious CVID-associated conditions were reported among 46.2% of the 990 patients, with significantly more among +AC patients (69.4%) compared to -AC patients (43.5%; OR = 2.9; 95%-CI: 1.9–4.6, $P < 0.001$) (Table 3). CVID-associated complications that were significantly increased included lymphoproliferation (OR = 3.1, 95%-CI: 3.1–7.3, $P < 0.001$), granulomatous disease (OR = 2.8, 95%-CI: 1.5–5.2, $P = 0.001$), lymphomas (OR = 2.7, 95%-CI: 1.1–6.4, $P = 0.026$), hepatic disease (OR = 2.5; 95%-CI: 1.3–5, $P = 0.004$), enteropathy (OR = 2.1, 95%-CI: 1–4.2, $P = 0.049$), and lung disease described as interstitial, granulomatous, or nodular (OR = 2.2, 95%-CI: 1.1–4.4, $P = 0.036$). Neither bronchiectasis nor inflammatory bowel disease (IBD) was significantly more common in +AC patients compared to -AC patients ($P = 0.578$, and $P = 0.567$, respectively). Other CVID-associated manifestations (nodular regenerative hyperplasia, granulomatous hepatitis, other hematologic malignancy) were uncommonly reported in the cohort (all $< 1.5\%$), and there were no differences between +AC and -AC patients.

Other forms of autoimmunity were also reported in 14.3% of the 990 patients (Table 4). Overall, these conditions were significantly more common among +AC patients (26.7%) than -AC patients (12.9%, OR = 2.5, 95%-CI: 1.5–4, $P < 0.001$); this was mostly attributed to increased organ-specific autoimmunity in +AC patients (21.8%), as compared to -AC patients (8.8%; OR = 2.9, 95%-CI: 1.7–4.9, $P < 0.001$). The organ-specific autoimmune conditions increased among +AC patients included vitiligo (OR = 8.2, 95%-CI: 2.9–23.1, $P < 0.001$), type I diabetes (OR = 6.6, 95%-CI: 2–21.1, $P = 0.002$), autoimmune hepatitis (OR = 5.6, 95%-CI: 2–15.6, $P = 0.001$), and celiac disease (OR = 3.9, 95%-CI: 1.5–10.5, $P = 0.006$). Systemic autoimmunity and vasculitis were not more common in the +AC group compared to the -AC group ($P = 0.923$, $P = 0.538$, respectively).

Discussion

Autoimmune cytopenias were reported in 10.2% of 990 CVID patients in the USIDNET Registry. This prevalence of autoimmune cytopenia is strikingly higher than among the general population, in whom ITP has been estimated to affect between 8 and 12 in 100,000 [14]; AIHA between 1 and 17 per 100,000 [15, 16]; and autoimmune neutropenia 1 in 100,000, among in children aged 1 to 10 years [17]. Compared to the USIDNET Registry, other CVID patient registries report higher prevalence of autoimmune cytopenias: a French report of 408 CVID patients and a US cohort of 473 CVID patients noted one or more autoimmune cytopenia in 14 to 18% of patients [4, 8, 18]. While 13.2 and 14.2% of CVID patients had a diagnosis of ITP in the French and New York cohorts respectively, only 7.4% were noted as having had ITP in USIDNET. AIHA or hemolytic anemia (4.3%) was also less commonly reported in the USIDNET Registry as compared to the French (5.5%) or New York studies (7%) [4, 8]. Prevalence of autoimmune neutropenia was 1% in this study and was also found to be low in the French and New York cohorts (3.2 and < 1%, respectively) [4, 8]. The enrichment of autoimmune complications at referral centers that see more complex cases of CVID is likely to explain the increased prevalence of these conditions. In contrast, the USIDNET cohort includes data from 173 physicians at 50 medical centers, potentially providing a better indicator of the true prevalence of these conditions in CVID.

We found no differences in demographics, age at diagnosis, or Ig values between patients with and without autoimmune cytopenias. This contrasts with the French and European CVID Registries, which found, respectively, that autoimmune cytopenia was associated with higher serum IgG levels [8], older age at CVID-onset, and lower serum IgA values [6].

These data confirm that CVID subjects with autoimmune cytopenias are more likely to have had other non-infectious CVID-associated complications (OR 2.9; 95%-CI: 1.9–4.6; $P < 0.001$), including interstitial lung disease [8, 11], enteropathy [6], hepatic disease [13], lymphoproliferation or splenomegaly [6, 8], and granulomatous disease [6, 12, 19]. With the exception of lymphoma and organ-specific autoimmunity, each of these conditions has been previously associated with either cytopenia or autoimmunity. The increased prevalence of these complications in the +AC CVID patients suggests that these conditions originate from the immune dysregulation and dysfunction contributing to their specific CVID phenotype. Further, the conditions that were increased in the +AC group have been associated with increased morbidity and mortality [3, 4, 18]. As the first episode of autoimmune cytopenia most often develops early in the course of CVID [8–10, 19, 20], autoimmune cytopenia may predict a more complicated course, necessitating closer monitoring for various non-infectious complications.

The likelihood of having bronchiectasis, inflammatory bowel disease, and systemic autoimmunity was not increased among patients with autoimmune cytopenia compared to those without. In the French cohort of CVID patients, investigators similarly found no association between systemic autoimmunity (including Sjogren's, RA, and SLE) and autoimmune cytopenia in CVID [8]. In the European CVID cohort ($N = 902$), investigators did not find a significant association between bronchiectasis and autoimmunity (not limited

to cytopenia) [6]. It might be expected that bronchiectasis would not be significantly associated with autoimmune cytopenias in our registry and other CVID cohorts; bronchiectasis is correlated with chronic or repeated pulmonary infections, and not with immune dysregulation [3, 6, 21].

This study has several limitations. Almost one third of subjects with a diagnosis of CVID were excluded from these analyses due to lack of IgA and/or IgM less than 2 standard deviations below the mean, in accordance with recent international guidelines [1]. We also acknowledge that an autoimmune basis for the thrombocytopenia or neutropenia observed is difficult to define. Cytopenias in CVID may result from hypersplenism, chronic liver disease, malignancy, recurrent or chronic infections, adverse effects to medications, or nutrient deficiencies due to malabsorption; however, testing for anti-platelet or anti-neutrophil antibodies are not widely available and often have poor sensitivity and/or specificity [22–24]. Thus, ITP and autoimmune neutropenia are diagnoses of exclusion, made in patients with isolated peripheral thrombocytopenia or neutropenia without other apparent cause [22, 23, 25]. As we have only included the physician-designated autoimmune cytopenia diagnoses, we may have underestimated the incidence of these disorders in this cohort.

In conclusion, among 990 CVID patients from the USIDNET Registry, autoimmune cytopenias were commonly reported. Those with autoimmune cytopenia were likely to have other CVID-associated conditions that are associated with increased risk of morbidity and mortality, including interstitial lung disease, enteropathy, hepatic disease, lymphoproliferation, lymphoma, granulomatous disease, and organ-specific autoimmunity [3, 4]. Prospective studies are necessary to validate whether a diagnosis of autoimmune cytopenia in CVID may predict a more complicated disease course with worse prognosis.

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Table 1

Prevalence of autoimmune cytopenias reported in 990 patients with common variable immunodeficiency in the USIDNET Registry*

Autoimmune cytopenia	N (%)
Any autoimmune cytopenia	101 (10.2%)
Autoimmune cytopenia in 2 cell lines	38 (3.8%)
Autoimmune cytopenia in 3 cell lines	4 (0.4%)
Evan's syndrome	16 (1.6%)
Immune thrombocytopenia	73 (7.4%)
Hemolytic anemia	45 (4.5%)
Autoimmune hemolytic anemia	11 (1.1%)
Autoimmune neutropenia	10 (1%)

* Diagnoses are presented as entered by contributors to the USIDNET Registry

Table 2

Comparison of demographics and immunoglobulin values of CVID patients with and without autoimmune cytopenia in the USIDNET Registry

		+ AC (N = 101)	–AC (N = 889)	<i>p</i> ^a
Gender N(%)	Female	49 (48.5%)	484 (54.4%)	0.260
	Male	52 (51.5%)	405 (45.6%)	0.260
	Caucasian	77 (93.9%)	621 (95.8%)	0.430
Race N(%)	African-American	5 (6.1%)	23 (3.5%)	0.246
	Asian	0 (0%)	4 (0.6%)	n/a
	Not specified	19 (18.8%)	241 (27%)	0.076
Ethnicity N(%)	Hispanic	3 (3.7%)	23 (3.5%)	0.918
Age ^b , years	CVID symptom onset	16 (10–31)	16 (5–32)	0.465
Median (IQR)	Last entry	30 (20–44)	36 (17–53)	0.124
Ig levels ^c , mg/dL	IgG	339 (206–625)	372 (159–592)	0.974
	IgA	8 (7–17)	11 (7–33)	0.163
Median (IQR)	IgM	28 (16–56)	26 (11–47)	0.203

+AC patients with autoimmune cytopenia, –AC patients without autoimmune cytopenia, CVID common variable immunodeficiency, Ig immunoglobulin

^a *P* value was determined using Chi-square calculation (categorical variables) and Student's *t* test (continuous variables)

^b Age at symptom onset was available for 73.7 and 59.3% of CVID patients with and without autoimmune cytopenia, respectively

^c Ig values were available for 98.3 and 99.1% of entries for patients with and without autoimmune cytopenia, respectively. Lowest available IgG was chosen for inclusion. It was not known whether IgG values were taken on or off therapy. IgA and IgM associated with IgG value were then included in analysis

n/a *P* value cannot be calculated with the values being zero

Table 3

Comparison of additional CVID-associated diagnoses among CVID patients with (+AC) and without autoimmune cytopenia (-AC) in the USIDNET Registry *

	CVID cohort (N = 990) N (%)			+AC (N = 99) N (%)	-AC (N = 891) N (%)	OR	95% CI	P
Any CVID-associated condition	457 (46.2%)	149 (15.1%)	53 (5.4%)	10 (9.9%)	387 (43.5%)	2.9	(1.9–4.6)	< 0.001
Pulmonary ^a	149 (15.1%)	53 (5.4%)	10 (9.9%)	13 (12.9%)	127 (14.3%)	1.7	(1–2.8)	0.048
ILD/granuloma/nodules	111 (11.2%)	103 (10.4%)	55 (5.6%)	62 (6.3%)	43 (4.8%)	2.2	(1.1–4.4)	0.036
Bronchiectasis	103 (10.4%)	55 (5.6%)	62 (6.3%)	13 (12.9%)	98 (11%)	1.2	(0.6–2.2)	0.578
Gastrointestinal ^a	103 (10.4%)	55 (5.6%)	62 (6.3%)	13 (12.9%)	90 (10.1%)	1.3	(0.7–2.4)	0.393
Enteropathy ^b	55 (5.6%)	10 (9.9%)	13 (12.9%)	7 (6.9%)	45 (5.1%)	2.1	(1–4.2)	0.049
IBD ^c	62 (6.3%)	13 (12.9%)	7 (6.9%)	6 (5.9%)	57 (6.4%)	0.8	(0.3–1.9)	0.567
Hepatic	61 (6.2%)	21 (2.1%)	40 (4%)	196 (19.8%)	48 (5.4%)	2.6	(1.3–5)	0.004
Specific diagnoses ^d	21 (2.1%)	17 (1.7%)	136 (13.7%)	49 (48.5%)	14 (1.6%)	4.7	(1.8–11.8)	0.001
Non-specific ^e	40 (4%)	104 (10.5%)	67 (6.8%)	43 (4.3%)	34 (3.8%)	1.6	(0.7–3.9)	0.310
Lymphoproliferation ^f	196 (19.8%)	104 (10.5%)	67 (6.8%)	7 (6.9%)	147 (16.5%)	4.8	(3.1–7.3)	< 0.001
Lymphoid hyperplasia	17 (1.7%)	136 (13.7%)	67 (6.8%)	43 (4.3%)	13 (1.5%)	2.8	(0.9–8.7)	0.079
Lymphadenopathy	136 (13.7%)	104 (10.5%)	67 (6.8%)	7 (6.9%)	100 (11.2%)	4.4	(2.8–6.9)	< 0.001
Splenomegaly	104 (10.5%)	67 (6.8%)	43 (4.3%)	7 (6.9%)	76 (8.5%)	4.1	(2.5–6.7)	< 0.001
Granulomatous disease	67 (6.8%)	43 (4.3%)	31 (3.1%)	13 (1.3%)	52 (5.8%)	2.8	(1.5–5.2)	0.001
Hematologic malignancy	43 (4.3%)	31 (3.1%)	13 (1.3%)	0 (0%)	36 (4%)	1.8	(0.8–4.1)	0.184
Lymphoma	31 (3.1%)	13 (1.3%)	0 (0%)	0 (0%)	24 (2.7%)	2.7	(1.1–6.4)	0.026
Other ^g	13 (1.3%)	0 (0%)	0 (0%)	0 (0%)	13 (1.5%)	0.0	n/a	n/a

CVID common variable immunodeficiency, ILD interstitial lung disease, IBD inflammatory bowel disease, NRH nodular regenerative hyperplasia

* Diagnoses are presented as entered by contributors to the USIDNET Registry

^a Given the broad range of non-specific diagnoses, reporting of pulmonary and gastrointestinal diagnoses were limited to those that were specific

^b Diagnoses include enteropathy, gastroenteropathy, enterocolitis, lymphocytic colitis, chronic gastritis, atrophic gastritis, gastroenteritis, enteritis, duodenitis, or bacterial overgrowth

^c Diagnoses include inflammatory bowel disease, Crohn's disease, or ulcerative colitis

^d Diagnoses include autoimmune hepatitis, NRH, or granulomatous hepatitis

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Diagnoses include hepatomegaly or liver function abnormalities
Lymphoproliferation associated with a diagnosis of lymphoma was excluded from this category
Diagnoses included leukemia, myelodysplasia, myeloproliferation, multiple myeloma, or monoglonal gammopathy

Table 4

Comparison of autoimmune conditions among CVID patients with (+AC) or without autoimmune cytopenia (−AC) in the USIDNET Registry^{*}

Autoimmune conditions	CVID cohort (N = 990) N (%)	+AC (N = 101) N (%)	−AC (N = 889) N (%)	OR	95% CI	P
Any other autoimmunity	142 (14.3%)	27 (26.7%)	115 (12.9%)	2.5	(1.5–4)	< 0.001
Systemic	41 (4.1%)	4 (4%)	37 (4.2%)	0.9	(0.3–2.7)	0.923
Organ-specific ^a	100 (10.1%)	22 (21.8%)	78 (8.8%)	2.9	(1.7–4.9)	< 0.001
Systemic autoimmunity						
RA	18 (1.8%)	2 (2%)	16 (1.8%)	1.1	(0.2–4.9)	0.898
SLE	9 (0.9%)	2 (2%)	7 (0.8%)	2.5	(0.5–12.4)	0.248
Vasculitis	13 (1.3%)	2 (2%)	11 (1.2%)	1.6	(0.4–7.4)	0.538
Other ^b	16 (1.6%)	0 (0%)	16 (1.8%)	0		
Integument	42 (4.2%)	9 (8.9%)	33 (3.7%)	2.5	(1.2–5.5)	0.017
Psoriasis	26 (2.6%)	2 (2%)	24 (2.7%)	0.7	(0.2–3.1)	0.670
Vitiligo	15 (1.5%)	7 (6.9%)	8 (0.9%)	8.2	(2.9–23.1)	< 0.001
Other autoimmune ^c	1 (0.1%)	0 (0%)	1 (0.1%)	0.0		
Autoimmune enteropathy	22 (2.2%)	6 (5.9%)	16 (1.8%)	3.4	(1.3–9)	0.012
Autoimmune hepatitis	16 (1.6%)	6 (5.9%)	10 (1.1%)	5.6	(2–15.6)	0.001
Endocrine	26 (2.6%)	6 (5.9%)	20 (2.2%)	2.7	(1.1–7)	0.035
Type 1 diabetes	12 (1.2%)	5 (5%)	7 (0.8%)	6.6	(2–21.1)	0.002
Autoimmune thyroiditis	14 (1.4%)	1 (1%)	13 (1.5%)	0.7	(0.1–5.2)	0.705
Ocular ^d	8 (0.8%)	1 (1%)	7 (0.8%)	1.3	(0.2–10.3)	0.830

CVID common variable immunodeficiency, RA rheumatoid arthritis, SLE systemic lupus erythematosus

^{*} Diagnoses are presented as entered by contributors to the USIDNET Registry

^a Includes diagnoses listed in the table under “Integument,” “Autoimmune enteropathy,” “Autoimmune hepatitis,” “Endocrine,” and “Ocular”

^b Diagnoses include mixed connective tissue disease, spondyloarthropathy, scleroderma, or dermatomyositis

^c Diagnoses include lichen planus, or alopecia areata

^d Diagnoses include uveitis, iritis, or iridocyclitis