Rheumatological Diseases in Patients with Inborn Errors of Immunity in the USIDNET Registry

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Abstract

Purpose

There is a gap in clinical knowledge regarding associations between specific inborn errors of immunity (IEIs) and rheumatological diseases. In this study, we report the frequency of rheumatological conditions in a large cohort of patients with IEI using the USIDNET (United States Immunodeficiency Network) registry.

Methods

We used the USIDNET registry to conduct the analysis. We included all IEI patients within the registry for whom a diagnosed rheumatological disease was reported.

Results

The total number of patients with IEI in our query was 5058. Among those, 278 (5.49%) patients had a diagnosis of rheumatological disease. This cohort included 172 (61.8%) female and 106 (38.2%) male patients. Rheumatologic complications were highest in the interferonopathies (66.6%), autoimmune lymphoproliferative syndrome (ALPS) (13.7%) and Immunoglobulin G subclass deficiency (IgGSD) (11.11%). Additionally, disease patterns were noted to be different in various IEI disease groups. Inflammatory myopathies were the most common rheumatologic condition in patients with X-linked agammaglobulinemia (1.65%), Sjogren's syndrome was the most common rheumatology disease reported in ALPS patients (6.85%) and systemic lupus erythematosus was the most common rheumatology disease in in patients with Chronic mucocutaneous candidiasis(CMC) (7.41%). Rheumatoid arthritis (RA) report rate was highest in patients with IgGSD (3.70%), specific antibody deficiency (3.66%), and ALPS (2.74%).

Conclusion

This study reports that rheumatologic diseases are frequently observed in patients with IEI. The frequency of different rheumatological disease was variable based on the underlying diagnosis. Clinicians caring for patients with IEI should be vigilant to monitor for rheumatologic complications.

Introduction

Inborn errors of immunity (IEIs) encompass more than 400 heterogeneous congenital disorders that cause impaired immune function[1]. Although the individual prevalence of individual IEIs are largely unknown, the collective prevalence of IEIs is thought to be 1 in 1000 to 2000 individuals in the US[2]. Since the first documentation of these disorders in 1952 by Bruton[3], described complications have evolved from only increased susceptibility to infections to the recognition of additional risks for autoimmunity, autoinflammation, atopy and cancer predisposition in many disorders.

A French Primary immunodeficiency (PID) registry study showed a significant increase (120 times) in the risk of developing autoimmune cytopenia as well as an increase (80 times) in the risk of inflammatory bowel disease (IBD) in children with IEI [4]. The same study showed ten times higher risk of autoimmunity in this population as well. As expected, the presence of autoimmune complications resulted in increased mortality. Interestingly, T cell defects and common variable immunodeficiency (CVID) were found to carry the highest risk of autoimmunity. When CVID population in the United States Immunodeficiency Network (USIDNET) was evaluated, 5.9% of CVID patients were found to have a physician-diagnosed rheumatologic disease[5]. Furthermore, female gender was identified more frequently in patients with rheumatologic conditions and CVID in the US[5]. There are still many unknowns in demographics and biological risk stratification of patients with IEI when considering rheumatologic diseases.

Although it is shown that primary antibody deficiencies are associated with increased autoimmunity and rheumatologic diseases [6–9], there is still a large gap in knowledge about specific disease associations and outcomes. Limited studies were done on specific IEIs showed interesting findings. For example, the frequency of arthritis was found to be between 10–30% in patients with X-linked Agammaglobulinemia(XLA)[10]. Similarly, vasculitis was a well-documented complication of Wiskott-Aldrich Syndrome (WAS) and an association was found between systemic lupus erythematosus (SLE) and early complement deficiencies [11, 12]. These findings suggest that similar associations may be present with other IEIs and more work is needed to describe these complications. Strikingly, it is not uncommon to find rheumatologic complications prior to IEI diagnosis as well[13]. In this study, we aimed to evaluate the frequency of rheumatologic conditions in USIDNET registry. This information can be helpful in guiding clinicians to risk stratify patients with IEI and hopefully reduce morbidity and mortality with early diagnosis and treatment of the rheumatologic diseases.

Methods

We performed a retrospective analysis of data obtained from the USIDNET registry. The U.S. Immunodeficiency Network (USIDNET), a program of the Immune Deficiency Foundation (IDF), is supported by a cooperative agreement, U24AI86837, from the National Institute of Allergy and Infectious Diseases (NIAID). We obtained de-identified patient demographic data including race, gender, age, living status, stem cell transplant status, rheumatologic and IEI diagnoses as well as underlying genetic mutation in patients with rheumatologic diagnoses. Due to a limited number of observations, we chose not to perform comparative statistical analysis.

Clinical data

Inflammatory arthritis was described as any form autoimmune/autoinflammatory arthritis including rheumatoid arthritis, juvenile idiopathic arthritis and psoriatic arthritis. In addition to arthritis, our cohort included patients with SLE, inflammatory myopathies (dermatomyositis and polymyositis), vasculitis, Sjogren's syndrome as well as systemic sclerosis. Patients with nonspecific arthritis and degenerative arthritis were excluded from the cohort. Sjogren's syndrome diagnosis covered both primary and secondary Sjogren's syndrome. Patients with RA and JIA diagnosis at the same time were only included in JIA category. In order to maintain accuracy of data, patients with both SLE and vasculitis were counted only as SLE given vasculitis can be part of the clinical presentation of SLE. Similarly, patients with psoriatic arthritis and RA were counted as only psoriatic arthritis. Our cohort had 2 patients with dermatomyositis and systemic sclerosis which is typically consider an overlap syndrome, these diagnoses were counted twice in total, one in each category.

Results

Patient Demographics

A total of 5058 patients were reported in the USIDNET registry at the time of data query. Among those, 278 (5.49%) patients had both IEI and at least one rheumatologic disease diagnosis (Table 1). Caucasian ethnicity was the most reported race in our cohort. 62% of patients were female.

Distribution of rheumatologic diseases in USIDNET cohort

We first investigated the frequency of rheumatologic diseases in the USIDNET population (Figure 1). Inflammatory joint disease (includes RA, JIA and psoriatic arthritis) was the most common rheumatologic condition reported (2.08%) (table 2). ALPS was reported to have the highest rate of inflammatory arthritis (4.11%) (table 3). Following arthritis, the second most common rheumatologic condition in our cohort was vasculitis (1.01%). As expected, interferonopathies and WAS were the IEIs with the highest rate of vasculitis reported.

In addition to frequently seen rheumatologic conditions, rare rheumatologic diseases were also reported in the USIDNET registry. Among these, SLE and Sjogren's showed similar rates (0.67% and 0.69%, respectively). Interestingly, the rate of SLE

was highest in chronic mucocutaneous candidiasis (CMC) (7.41%) followed by complement deficiencies (3.57%). In contrast, Sjogren's was not reported in these conditions. Instead, IgG subclass deficiencies and ALPS had the highest reported rate of Sjogren's (7.41% and 6.85%, respectively). As expected, systemic sclerosis and inflammatory myopathies had the lowest report rate in the cohort (0.19% and 0.24%, respectively). Reported systemic sclerosis rate was highest in familial HLH, whereas inflammatory myopathies had the highest frequency in agammaglobulinemia (2.99% and 1.65%, respectively) (table 3).

After identifying the rates of rheumatologic diseases in our cohort, we next investigated the specific IEI diagnosis and associated rheumatologic diseases. Interestingly, certain IEIs were noted to have higher rate of specific rheumatologic conditions.

Distribution of rheumatologic diseases in specific IEI populations

Immunodeficiencies affecting cellular and humoral immunity:

Overall, rheumatologic disease frequency in this group was noted to be 1.7%. At the time of the query, the USIDNET cohort had 339 severe combined immunodeficiency (SCID), 92 nonspecific combined immunodeficiency (CID) and 156 hyper IgM syndrome (HIGM) patients. Among those, 1 SCID (0.29%) patient was reported to have inflammatory arthritis. No other rheumatologic diagnoses were reported in this group. Interestingly, nonspecific CID patients were reported to have a higher rate of arthritis (3.26%), followed by vasculitis (2.17%), SLE (1.09%) and inflammatory myopathies (1.09%). Rheumatologic disease rate in HIGM patients was 1.28%, evenly distributed between inflammatory arthritis and vasculitis.

Combined immunodeficiency with associated or syndromic features

The USIDNET cohort included 246 WAS, 102 Hyper IgE syndrome (HIES) and 523 DiGeorge syndrome patients. The rheumatologic condition with highest rate was vasculitis (6.5%) in WAS. Systemic sclerosis and arthritis were reported with lower rates in this group (0.41% and 0.41% respectively). DiGeorge syndrome patients had a lower rate of arthritis (0.19%) and systemic sclerosis (0.19%) and none had vasculitis. It was noted that 1.96% of HIES patients were diagnosed with SLE and 0.98% of HIES patient were reported to have vasculitis.

Predominantly antibody deficiencies:

Our query included 82 SAD, 425 agammaglobulinemia, 1739 CVID and 60 specific IgA deficiency patients (SIgAD). Patients with SIgAD had a lower rate of rheumatologic disease in our cohort with one case (1.67%) of reported arthritis. Interestingly, patients with agammaglobulinemia showed an impressively different profile with highest rate of inflammatory myopathies in the entire cohort (1.65%). This was followed by arthritis (1.41%), systemic sclerosis (0.47%), vasculitis (0.47%) and SLE (0.24%).

CVID was the predominant immunodeficiency (34.4%) reported in the USIDNET cohort. Among patients with CVID, 7.36% had at least one type of rheumatologic disease. The most common rheumatologic disease reported was inflammatory arthritis (4.03%), followed by Sjogren's (1.27%), systemic sclerosis (0.92%) and vasculitis (0.86%). Moreover, inflammatory myositis (0.17%) and SLE (0.12%) were also reported in patients with CVID. Similar to CVID, arthritis was also the most common rheumatologic disease in SAD patients (3.66%), followed by Sjogren's (2.44%) and SLE (1.22%). Additionally, arthritis remained the most common rheumatologic disease in patients with hypogammaglobulinemia (3.45%). Similar to other antibody deficiencies, Sjogren's and vasculitis were also reported in this group (0.99% and 0.99% respectively).

Disease of immune dysregulation:

Patients with immune dysregulation were reported to have arthritis (3.37%), vasculitis (3.37%), Sjogren's (2.24%) and systemic sclerosis (1.12%). Among 64 patients with HLH, 3 patients (4.68%) were reported to have a rheumatologic disease with 2 having systemic sclerosis and one patient with arthritis. Interestingly, 13.69% of ALPS patients had a rheumatologic condition and the majority of these cases were reported to be Sjogren's syndrome (50%).

Congenital defects of phagocyte number, function or both:

Chronic granulomatous disease (CGD) was the second most commonly reported IEI in the USIDNET registry. We found that 2.05% of CGD patients had been diagnosed with a rheumatologic disease. SLE was the most common (1.49%) rheumatologic condition in CGD patients followed by vasculitis (0.37%) and arthritis (0.19%).

There were 57 reported cases of GATA2 defects in USIDNET. Among those, 4 patients (7.02%) were reported to have a rheumatologic diagnosis. Reported conditions were vasculitis (50%), arthritis (25%) and systemic sclerosis (25%). In contrast to CGD, there were no reported cases of SLE in patients with GATA2 defect.

Defects in intrinsic and innate immunity:

The USIDNET cohort included 27 CMC patients. Interestingly, SLE was the only rheumatologic condition reported in patients with CMC (7.41%).

Auto-inflammatory disorders:

Three patients were reported to have interferonopathies in the USIDNET cohort. Interestingly 2 of them (66.67%) were reported to have vasculitis. No other rheumatologic diseases were reported in this group.

Complement deficiencies:

The USIDNET cohort had 28 patients with reported complement deficiencies. The overall frequency of rheumatologic disease was 7.14 % with reported SLE (3.57%), vasculitis(3.57%) and arthritis (3.57%).

Our query did not have patients with a rheumatologic diagnosis from IEI groups of defects in bone marrow failure and phenocopies of IEI.

Discussion

This is the first USIDNET study to our knowledge to investigate the frequency of rheumatologic diseases among the various IEIs. Although it is widely accepted that IEI has higher frequency of autoimmune diseases in comparison to the general population, it is unknown if certain rheumatologic diagnoses are associated with specific IEI types. Our results showed that the frequency of rheumatologic diagnoses have a wide spectrum in IEI and differ even in the same IEI category. For example, although inflammatory arthritis was the most commonly reported rheumatologic disease in CVID; inflammatory myopathies had the highest rate in patients with agammaglobulinemia. These differences could reflect the unknown differences in pathophysiology of autoimmunity in individual IEIs. In contrast to previous work on USIDNET CVID population, we did not detect a significant female dominance in our cohort [5]. This could be due to a larger sample size with other IEI included.

Frequencies of rheumatologic diseases are limited to small cohorts in the US, however rates of rheumatologic diseases in the USIDNET cohort was found to be higher in all rheumatologic diseases investigated (Table 2). For example, frequency of rheumatoid arthritis in the US was reported in the range of 0.5-1%[14, 15] with much smaller frequencies for JIA(0.086%)[16, 17] and psoriatic arthritis(0.1%-0.25%)[18, 19]. Whereas, arthritis rate in the USIDNET cohort was found to be 2.08%. Similar pattern was noted with SLE. Reported US frequencies of SLE was between 0.08%-0.15%[20–22]. Interestingly, the reported SLE rate in USIDNET was 0.67%. Limited studies showed frequency of systemic sclerosis in the US between 0.01% – 0.02%[23, 24]. The rate of systemic sclerosis in our cohort was 0.20%. Similarly, estimated frequency of inflammatory myopathies in the US was reported as 0.01% – 0.02%[25, 26], whereas the reported rate of this condition was 0.24% in our cohort. However, these results should be analyzed in the background of many limitations related to USIDNET cohort and comparison of small cohort studies.

There are multiple limitations to this study. Most importantly, although USIDNET is the largest cohort of reported IEI patients, it may not completely reflect the real-life population. More specifically, it is possible that patients with both IEI and rheumatologic

disease were overrepresented in our query considering the majority of IEI cases are followed in tertiary care centers if they have a rheumatologic condition as well. Another limitation is the difficulty of comparing the general population with the USIDNET cohort from rheumatologic disease frequency standpoint. There is a significant gap in knowledge in the epidemiology of rheumatologic diseases in the general population; therefore, comparison between the USIDNET cohort and the general population cannot be made based on limited studies, especially for vasculitis, Sjogren's and systemic sclerosis. Lastly, this is a retrospective study involving multiple centers across the US which could introduce bias in terms of missing data or variability of clinical practice in diagnosing patients with rheumatological disease. Epidemiology of rheumatologic disease and IEIs remain as an area that require improvement in the field of immunology.

Conclusions

Our results conclude that although the frequency of rheumatologic disease in IEI remains unknown, the rates of reported rheumatologic diseases in the USIDNET registry demonstrates a susceptibility to rheumatologic diseases in IEI with different rates in individual IEIs. Further studies would provide guidance to clinicians for detection of rheumatologic conditions earlier, therefore improving outcomes.

Declarations

Funding: None

Conflicts of interest/Competing interests: None

Availability of data and material: Non-applicable

Code availability: Not applicable

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Tables

Table 1. Features of subjects

	IEI + Rheum. dz in USIDNET cohort N = 278	USIDNET cohort* N= 5,482
Sex, Female, n (%)	172 (62)	2,120 (39)
Race, n (%)		
Caucasian	227 (82)	3,766 (69)
AA	16 (6)	293 (5)
Asian	6 (2)	100 (2)
Mixed race	5 (2)	154 (3)
Unknown	23 (8)	1,125 (21)
American Indian	1 (0)	42 (1)
Ethnicity, Hispanic, n (%)	11 (4)	367 (7)
Living, yes, n (%)	241 (87)	5,021 (92)
Stem cell transplant, n (%)	21 (8)	700 (13)
Specified genetic mutation, n (%)	83 (30)	2,511 (46)

*Data extracted on 05/01/2020, from https://usidnet.org/registry-data/stats-registry-enrollment/. This data reflects USIDNet patients with clinical visit data.

Table 2. Distribution of rheumatologic diseases in USIDNET cohort

Disease	USIDNET cohort (%)
Arthritis	2.08
SLE	0.67
Systemic sclerosis	0.20
Vasculitis	1.01
Sjogren's	0.69
Dermatomyositis/ polymyositis	0.24

Table 3. Distribution of rheumatologic diseases per individual IEIs

Disease	N	Inflammatory Arthritis (%)	SLE (%)	Systemic sclerosis (%)	Vasculitis (%)	Sjogren's (%)	Dermatomyositis/ polymyositis (%)	Total (%)
WAS	246	0.41	-	0.41	6.50	-	-	7.32
SAD	82	3.66	1.22	-	1.22	2.44	-	8.54
SCID	339	0.29	-	-	-	-	-	0.29
CMC	27	-	7.41	-	-	-	-	7.41
IFNpathy	3	-	-	-	66.67	-	-	66.67
PID+Myelodysplasia	57	1.75	-	1.75	3.51	-	-	7.02
ImmDysregulation	89	3.37	-	1.12	3.37	2.25	-	10.11
IgGSCD	27	3.70	-	-	-	7.41	-	11.11
SIgAD	60	1.67	-	-	-	-	-	1.67
Hypogam	203	3.45	0.99	-	0.99	0.99	-	6.40
HIGM	156	0.64	-	-	0.64	-	-	1.28
HIES	102	-	1.96	-	0.98	-	-	2.94
HLH	67	1.49	-	2.99	-	-	-	4.48
DiGeorge	523	0.19	-	0.19	-	-	-	0.38
Complement	28	3.57	3.57	-	3.57	-	-	10.71
CVID	1739	4.03	0.12	0.92	0.86	1.27	0.17	7.36
CID	92	3.26	1.09	-	2.17	-	1.09	7.61
CGD	536	0.19	1.49	-	0.37	-	-	2.05
Agam	425	1.41	0.24	0.47	0.47	-	1.65	4.24
ALPS	73	4.11	-	-	1.37	6.85	1.37	13.70

Supplemental table 1. Reported genes with pathogenic variants in PIDD patients with rheumatologic disease

Disease (N)	Gene
WAS (18)	WAS (5)
SAD (7)	CBS (1)
SCID (1)	IL7RA(1)
CMC (2)	STAT1 (2)
IFNpathy (2)	IFNGR1 (1), CECR1(ADA2)(1)
PID+Myelodysplasia (5)	GATA2 (5)
ImmDysregulation (9)	STAT3 (GOF) (1), LRBA(1), PI3KR1(1), STAT1 (GOF)(1), CTLA4(3)
IgGSCD	-
sIgAD	-
Hypogam	-
HIGM (3)	CD40LG (3)
HIES (6)	STAT3(4), PGM3(1)
HLH (4)	XIAP(2), UNC13D (1)
DiGeorge (2)	Del22q11.2 (2)
Complement (4)	C2 (1), C8 (1), SERPING1 (1)
CVID (144)	BTK (1), UNG (1), AIRE (1)
Combined (8)	DOCK8 (3)
CGD (11)	CYBB (6),NCF1(4), CYBA(1)
Agammaglobulinemia (18)	BTK (18)
ALPS (10)	AIRE (8), TNFRSF6 (ALPS-FAS) (1)

Figures

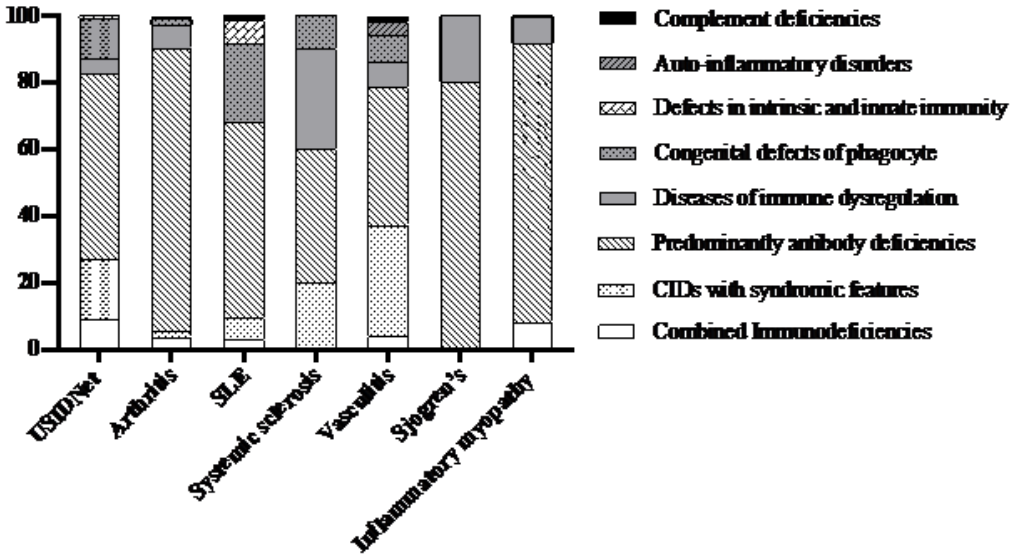

Figure 1

Distribution of IEIs among USIDNET and various rheumatic disorders