BMC Rheumatology

RESEARCH

Open Access

Rheumatologic manifestations in children with underlying inborn errors of immunity

Zohreh Saeidi[1], Sina Fadai[1], Mehrnaz Mesdaghi[2], Azadeh Zeinab Mirzaee[3,4], Samin Sharafian[2], Khosro Rahmani[4], Narges Eslami[2], Vadood Javadi Parvaneh[4], Mahsa Talebi[1], Zahra Chavoshzadeh[2*] and Reza Shiari[4*]

Abstract

Background and objective In recent years, many studies have been conducted on the possible link between rheumatologic diseases and inborn errors of immunity. Rheumatologic diseases may occur as manifestations of an underlying immunodeficiency disorder, and may appear before the more-common infectious manifestations more typically seen in immunodeficiency disorders. In this study, we have attempted to study such symptoms and uncover their relationship with inborn errors of immunity.

Methodology In this retrospective descriptive-analytical study, 381 cases of IEIs in children that were referred to Mofid Children's Hospital clinic between 2015 and 2019 were evaluated for eligibility to be enrolled in the study. Of these patients, 20 that had confirmed rheumatologic diagnoses were entered into the study. Patients' demographic and medical data, including age at disease onset, age at diagnosis and type of diagnosed rheumatologic and immunodeficiency disorders, parental consanguinity rate, and relevant laboratory findings were retrieved for study and analyzed.

Results Among 20 eligible patients, half of which were female and half were male, the average age at disease onset, average age at diagnosis of the underlying immunodeficiency disease and average age at diagnosis of the rheumatologic disease were 2.98 ± 1.56, 5.26 ± 3.45 and 3.58 ± 2.97, respectively. JIA made up 10 of the observed rheumatic diseases ("the JIA group"); the remaining 10 patients included SLE (3), FMF (2), juvenile dermatomyositis (2), MCTD (1), GPA (1) and reactive arthritis (1) ("the non-JIA group"). As for the underlying immunodeficiency disorders, CID was seen in 8 patients, followed by CVID (5), XLA (4), SIgAD (2) and CGD (1). The average age at onset of the disease and the average age at diagnosis of the rheumatologic disease were significantly lower in the JIA group than in the non-JIA group ($p < 0.05$).

Conclusions A plethora of rheumatologic manifestations may be observed in patients with IEIs; such manifestations should be actively sought out and treated in IEI patients.

Clinical trial number Not applicable.

Keywords Inborn error of immunity, Primary immunodeficiency disorder, Rheumatologic diseases, Combined immunodeficiency

*Correspondence:
Zahra Chavoshzadeh
Zahra_chavoshzadeh@yahoo.com
Reza Shiari
Shiareza@yahoo.com

Full list of author information is available at the end of the article

Introduction

Inborn errors of immunity (IEIs), formerly known as primary immunodeficiencies (PIDs), are a group of congenital diseases that qualitatively or quantitatively affect components of innate and adaptive immunity, causing various pulmonary, dermatologic, gastrointestinal, rheumatologic, autoimmune, hematologic and oncologic manifestations, many of which have been extensively studied [1–5]. Nearly 500 types of IEIs and 250 gene associations with IEIs have been discovered to date [6–8].

The IEI prevalence rate is estimated to be 4.4:100,000 in France [9], 5.6:100,000 in Australia [10], and 5.9:100,000 in the UK [11], though, depending on diagnostic criteria and data collection methodology, higher prevalence rates of up to 50.5:100,000 have also been reported in the literature [12]. The prevalence of selective IgA deficiency (SIgAD), which is one the more common IEIs, was estimated to be between 1:875 to 1:143 worldwide in a study [13]. On the other hand, the reported prevalence rate of SIgAD is 4.3% among JIA patients and 5.2% among SLE patients, which implies the existence of a meaningful association [14, 15]. A comparable association is also noted to exist between other antibody deficiency syndromes and autoimmune rheumatologic diseases. Similarly, the presence of component deficiencies in the classical complement pathway (e.g., C1, C2, C4) is a well-known genetic risk factor for SLE, and such deficiencies are often seen with increased prevalence in patients with rheumatoid arthritis as well [16–18]. On the other hand, in recent studies conducted on rheumatology patients, the prevalence of inborn errors of immunity (IEIs) was estimated to 14–22%, and the presence of an IEI was associated with a worse prognosis and a more severe disease outcome [19, 20].

In recent years, many studies have been conducted on the relationship between inborn errors of immunity (IEIs) and rheumatologic diseases; most have been on patients with immunodeficiency diseases with rheumatic manifestations as their primary or secondary symptoms. In many of these cases, these symptoms may appear before the more-common infectious manifestations that are very prevalent in patients with immunodeficiency disorders. The development of new biologic treatments for rheumatologic diseases may unmask previously undiagnosed immunodeficiencies, leading to symptomatic disease. Therefore, it is imperative that rheumatologists identify patients who present with common rheumatologic findings that may have an underlying immunodeficiency disorder [20].

Unfortunately, many IEIs are not identified or treated correctly. In IEIs, early diagnosis and treatment is critical in preventing complications [21]; in fact, a considerable percentage of patients with autoimmune diseases have an underlying IEI that may not be clinically related to the autoimmune disease, but can make the autoimmune disease more aggressive and confer a worse prognosis [20].

The aim of this study is to determine the prevalence of rheumatologic manifestations in immunodeficiency disorders among patients referred to rheumatology and clinical immunology clinics in Mofid Children's Hospital, as a step to ultimately help reduce diagnostic delay and prevent further disease complications.

Study method

In this retrospective descriptive-analytical study, children and teenagers under the age of 18 that presented or were referred to Mofid Children's Hospital with complaints of rheumatologic symptoms between March 2015 and March 2019 were considered for eligibility to be enrolled in this study. During this time period, 381 patients with established IEI diagnosing per the European Society for Immunodeficiencies (ESID) criteria [22] presented or were referred to Mofid Children's Hospital clinic, of which 20 had rheumatologic diagnoses that were either manifestations of, or worsened by, their underlying IEI that made them eligible to be entered into the study. All patients enrolled in our study had rheumatologic diagnoses established by an expert pediatric rheumatologist based on relevant symptoms (including but not limited to the presence of periodic fevers, skin rashes, oral aphthous ulcers, arthritis and serositis) in accordance with relevant diagnostic criteria and clinical practice guidelines.

After careful data collection, the patients' data was entered into the statistical software SPSS, v25, and analyzed. To compare qualitative data, chi-square and Fisher's exact tests were used. Subsequently, after verifying the assumption of normality for the data using the Kolmogorov-Smirnov test, Student's t test and variance analysis were used to compare data that followed a normal distribution, and Mann-Whitney and Kruskal-Wallis tests were used to compare data that did not (abnormal distribution). p values of less than or equal to 0.05 were considered significant.

Results

Demographic data

In this study of 381 patients under the age of 18 with established immunodeficiency disorder diagnoses that presented or were referred to Mofid Children's Hospital between March 2015 and March 2019, 20 patients with rheumatologic manifestations were enrolled into the study. The average age at first manifestation of the disease was 2.98 ± 1.56 years (range: 6mos-6yrs). The female-to-male ratio of enrolled patients was 1.

The age at diagnosis of the immunodeficiency disease was recorded for 19 patients and the average was 5.26 ± 3.45 years (range: 1-14yrs) and the average age at diagnosis of the rheumatologic disease was 3.58 ± 2.97

Table 1 Rheumatologic diseases by type

	Disease	Number (%)
JIA Group	JIA	10 (50%)
Non-JIA Group	SLE	3 (15%)
	FMF	2 (10%)
	Juvenile dermatomyositis	2 (10%)
	GPA	1 (5%)
	MCTD	1 (5%)
	Reactive Arthritis	1 (5%)

years (range: 6mos-13yrs). The average age at first manifestation of the disease and the average age at diagnosis of the rheumatologic disease was significantly lower in the JIA group as compared to the non-JIA group.

Of note, as expected in MENA countries with an established cultural practice of consanguineous unions, and therefore, a higher prevalence of recessive traits and disorders including IEIs, among 20 patients in our study, 16 (80%) were the result of a consanguineous parental union and 3 (15%) were not, and 1 had an unknown status. Parental consanguinity was unknown with regards to one of the enrolled patients. Equal rates of parental consanguinity were observed in both the JIA and non-JIA groups of the study.

The number of patients with low IgE was significantly higher in the JIA group, and the number of patients with high or normal IgE was significantly higher in the non-JIA group. In addition, the number and percentage of patients with high or normal IgM was significantly higher in the non-JIA group, and the number and percentage of patients with low IgM was significantly higher in the JIA group. There were no significant differences with regards to IgA and IgG levels between the JIA and non-JIA groups.

Table 2 Rheumatologic diseases by sex

	Male	Female	*p* value
JIA Group	8 (80%)	2 (20%)	0.007
Non-JIA Group	2 (20%)	8 (80%)	

The frequency of rheumatologic and immunodeficiency disorders

Among the studied patients, 10 (50%) had juvenile idiopathic arthritis (JIA) and 10 (50%) had rheumatologic diseases other than JIA, which included systemic lupus erythematosus (SLE) in 3 (15%), familial Mediterranean fever (FMF) in 2 (10%), juvenile dermatomyositis in 2 (10%), mixed connective tissue disorder (MCTD) in 1 (5%), granulomatosis with polyangiitis (GPA) in 1 (5%) and reactive arthritis in 1 (5%) (Table 1).

With respect to immunodeficiency disorders in enrolled patients, 8 (40%) had forms of combined immunodeficiencies (CIDs), 5 (25%) had forms of common variable immunodeficiencies (CVIDs), 4 (20%) had X-linked Agammaglobulinemia (XLA), 2 (10%) had selective IgA deficiency (SIgAD) and 1 (5%) had forms of chronic granulomatous diseases (CGDs).

There were no significant differences regarding the frequency of immunodeficiency disorders between the JIA and non-JIA groups, i.e., the aforementioned immunodeficiency disorders were evenly split among the two groups of the study.

Sex distribution

As stated previously, half of the studied subjects were female and the other half were male (Table 2). Sex distribution separated by rheumatologic diseases can be seen in Table 2; Fig. 1. As is evident, the number and percentage of boys in the JIA group and the number and percentage of girls in the non-JIA group were significantly

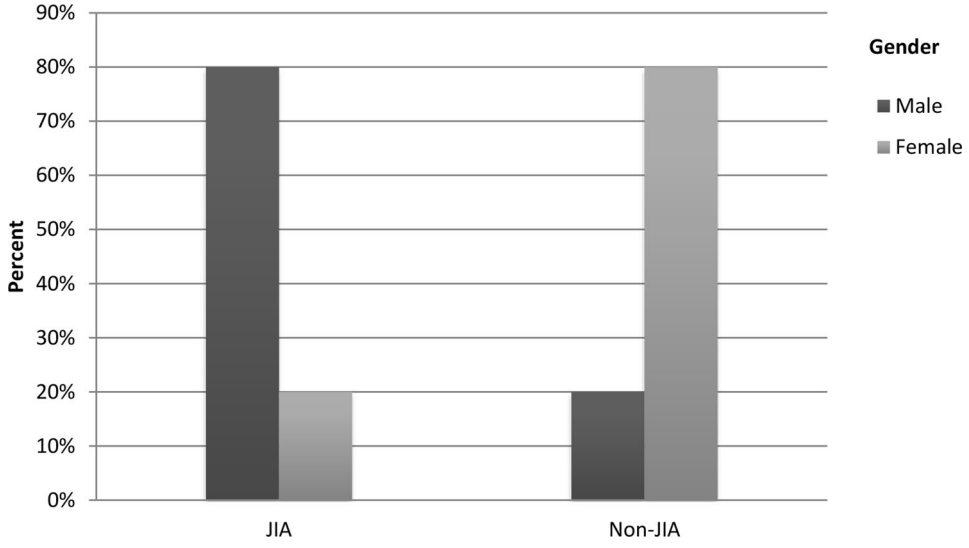

Fig. 1 Sex distribution in the JIA & non-JIA groups

Table 3 IEIs in the JIA & non-JIA groups

IEI	JIA	Non-JIA	
CID	3 (37.5%)	5 (62.5%)	MCTD (1)
			SLE (1)
			FMF (1)
			Juvenile dermatomyositis (2)
CVID	4 (80%)	1 (20%)	SLE (1)
XLA	3 (75%)	1 (25%)	GPA (1)
SIgAD	0 (0%)	2 (100%)	Reactive Arthritis (1)
			FMF (1)
CGD	0 (0%)	1 (100%)	SLE (1)

higher ($p = 0.007$). The patients' sex was observed to have no significant effects on the prevalence of immunodeficiency disorders ($p = 0.187$).

Immunodeficiency disorders in each patient group

As stated previously, half of the patients had JIA ("the JIA group") and the other half had diseases other than JIA ("the non-JIA group"). Immunodeficiency diseases separated by this division can be seen in Table 3; Fig. 2. Due to the small sample size, a clear pattern of association could not be definitively ascertained.

Presence of rheumatologic manifestation as first manifestation of underlying immunodeficiency disorder in each patient group

For 14 of the 20 enrolled patients, whether their rheumatologic symptom was the first manifestation of their underlying immunodeficiency disorder was noted; for the other 6, this data was not available. Of these 14 patients, which included 8 in the JIA group and 6 in the non-JIA group, 12 (85.7%) had rheumatologic symptoms as the first manifestation of their immunodeficiency disease, while 2 (14.3%) had other, non-rheumatologic symptoms, but developed rheumatologic symptoms over time (Fig. 3). Rheumatologic symptoms were the initial presentation in 8/8 (100%) of JIA patients and 4/6 (66.6%) of non-JIA patients. While the number and percentage of patients with an initial rheumatologic manifestation was higher in the JIA group, this difference was not found to be significant between the two groups.

Discussion

Inborn errors of immunity (IEIs), formerly known as primary immunodeficiency disorders (PIDs), can cause a multitude of symptoms in a patient, and these symptoms may involve basically any organ system [23]. Occasionally, rheumatologic symptoms and autoimmune diseases may occur as the result of an underlying inborn error of immunity, and may even predate the more-common infectious manifestations that characterize many IEIs [20]. Autoimmune and rheumatologic manifestations are seen with an increased prevalence in patients with underlying inborn errors of immunity [24, 25]; even in those whose autoimmune diseases are unrelated to a possible IEI, the presence of the latter, especially if undiagnosed and untreated, may exacerbate the primary condition and confer a worse prognosis [20].

In this study, we attempted to study different rheumatologic manifestations and their clinical courses in patients with underlying inborn errors of immunity (IEIs). As such, out of 381 patients with established IEI diagnoses per the ESID criteria [22] that presented or were referred to Mofid Children's Hospital clinic, 20 children and teenagers with complaints of rheumatologic symptoms between March 2015 and March 2019 were enrolled. Our patients were divided into two groups based on the presenting rheumatologic disease: Patients with JIA (the JIA group), which constituted half of all patients, including polyarthritis, oligoarthritis, and systemic juvenile idiopathic arthritis (SJIA) variants; and

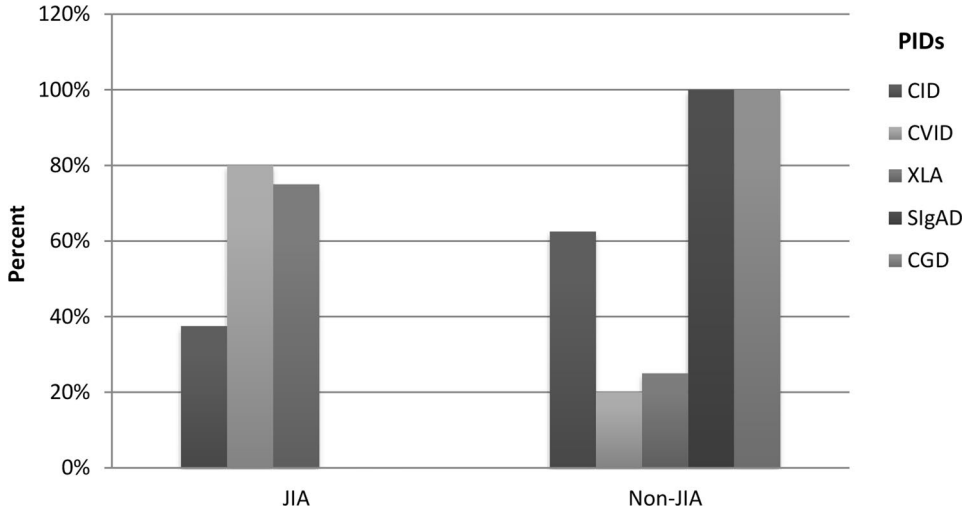

Fig. 2 Percentage of each IEI in the JIA & non-JIA Groups

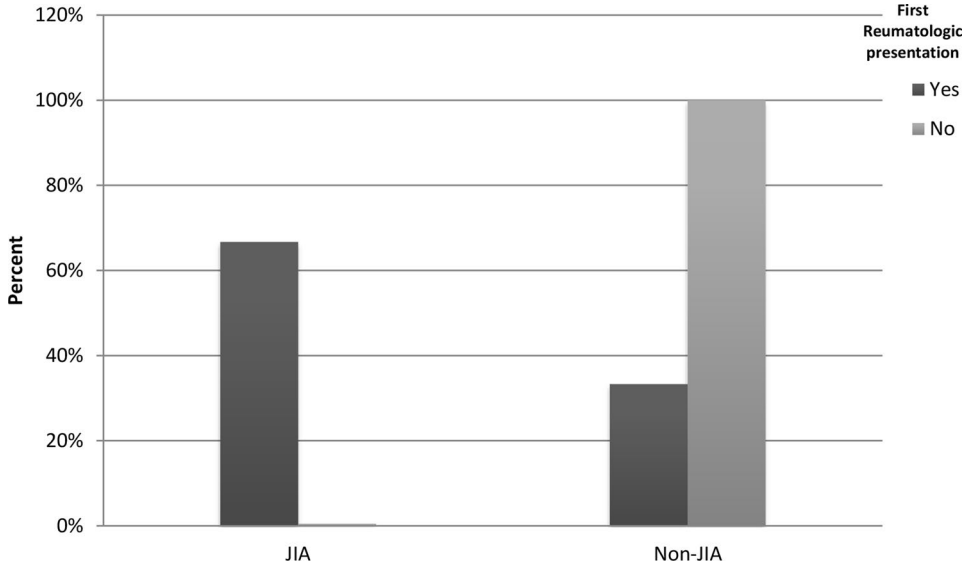

Fig. 3 Presence of rheumatologic symptom as initial manifestation of IEI in the JIA & non-JIA groups

patients that had non-JIA diseases, which made up the other half of all patients (the non-JIA group).

The average age at first manifestation of the disease was 2.98 ± 1.56 years in our study. The age at diagnosis of the immunodeficiency disorder was known for 19 of the 20 patients and the average was 5.26 ± 3.45 years. The average age at diagnosis of the rheumatologic disease was 3.58 ± 2.97 years. These findings are in contrast to those of studies by Spârchez et al. and Azizi et al., in which the age at onset of disease was higher as compared to our own; in the former, the age at manifestation of the immunodeficiency disease was 8 years among 117 patients, which included 84 JIA patients selected from a 1-year time-frame from a tertiary hospital center for rheumatology patients [19]. In the study by Azizi et al. that was conducted on 471 Iranian patients suffering from primary antibody deficiency (PAD) between 1999 and 2016, the average age at first manifestation of autoimmune disease was observed to be 7 years old [24]. In our study, the average age at first manifestation of the disease and the age at diagnosis of the rheumatologic disease was significantly lower in the JIA group as compared to the non-JIA group. This comparison was not done in the other aforementioned studies.

Among 20 patients who had rheumatologic symptoms in our study, the course of the disease was accurately documented in the medical charts of 14 patients, of which 12 (85.7%) had presented with rheumatologic symptoms as the initial manifestation of their underlying inborn error of immunity, and 2 (14.3%) had developed rheumatologic symptoms later on. Of the 12 patients that had presented with initial rheumatologic symptoms, 8 were in the JIA group and 4 were in the non-JIA group; of the 2 that did not present initially with a rheumatologic symptom but developed one over the course of their disease, both were in the non-JIA group. While the number and percentage of patients with an initial rheumatologic manifestation was higher in the JIA group, this difference was not found to be significant between the two groups.

As previously stated, half of the patients were female and the other half were male. The percentage of boys was significantly higher in the JIA group and the percentage of girls was significantly higher in the non-JIA group, but no significant differences were found with regards to the potential effects of patient sex on underlying immunodeficiency disorders; i.e., the observed immunodeficiency disorders were relatively evenly split between the sexes, with no obvious predilection towards a particular sex. In contrast to our study, the male to female ratio was approximately 2:1 in the study by Azizi et al., which may at least in part explain the differences in observations [24]. In the aforementioned study conducted by Spârchez et al., 60% of the patients with JIA were male, a finding that is similar to our own [19]. Likewise, in a retrospective study by Lim et al. on 86 cases of children with SLE that were hospitalized between 1997 and 2011 with the aim of identifying children with hypogammaglobulinemia and its risk factors, an overwhelming number of patients were female (91%), a sex disparity that is also appreciated in our non-JIA group [26].

In our study, JIA comprised 50% of all rheumatologic diseases that were observed in our patient groups; the other 50% (the non-JIA group) included SLE (15%), FMF (10%), juvenile dermatomyositis (10%), MCTD (5%), GPA (5%) and reactive arthritis (5%). The observed immunodeficiency disorders were as follows: 40% CID, 25% CVID, 20% XLA (Bruton's Agammaglobulinemia), 10% SIgAD and 5% CGD. There were no significant

differences regarding the frequency of immunodeficiency diseases between the JIA and non-JIA groups, i.e., the aforementioned immunodeficiency disorders were evenly split among the two groups of the study.

In a study similar to our own, but greater in scale, by Padem et al. on patients in the USIDNET (United States Immunodeficiency Network) registry who had rheumatologic manifestations, it was reported that such patients constituted 5.49% of all USIDNET patients at the time of the study. Despite our study's single-center nature and smaller scope, it is remarkable that a similar 5.24% of our total number of IEI patients (20 out of 381) also had rheumatologic diagnoses. The observed IEIs were different in the two studies; Padem et al. observed strong associations between rheumatologic diseases and interferonopathies, autoimmune lymphoproliferative syndrome (ALPS) and immunoglobulin G subclass deficiency (IgGSD), while we observed CVID, XLA, SIgAD, CGD and various CIDs. Several disease associations were observed in the aforementioned study, but unfortunately, similar associations cannot be accurately ascertained in our current study due to the limited sample size [27].

In a study by Fischer et al. that was conducted in France from September 2013 until February 2016 with the aim of evaluating autoimmunity and autoinflammation in PID patients, 2183 cases of PID were analyzed retrospectively. Per their findings, one or more complications of autoimmunity or autoinflammation were seen in 26.2% of the patients. The risk of autoimmune cytopenia, inflammatory bowel disease (IBD), and other autoimmune manifestations was at least 120, 80, and 10 times that of the general population, respectively, in PID patients. All types of PIDs were associated with autoimmune and [auto]inflammatory complications, though the most significant association was seen in T-cell related PIDs and CVID [28]. The findings of this study are in parallel with our own.

In the previously mentioned study of by Azizi et al., autoimmune disorders were found as the primary manifestation of immunodeficiency in 11 patients (2.5%), and a history of autoimmunity was observed in 125 patients (26.5%). The prevalence of autoimmune manifestations was higher in CVID (32%). Autoimmune gastrointestinal disorders and autoimmune cytopenias were the most common reported autoimmune disorders. Among patients with autoimmune manifestations, 87 (69.6%) had a history of only one autoimmune disorder, while 38 (30.4%) had a history of more than one of such autoimmune disorders [24].

Early diagnosis and proper management of IEIs are critical to prevent the occurrence of complications that may include secondary disorders, or exacerbation of previously established disorders, including rheumatologic ones [23, 24].

Limitations, suggestions and prospects

As a single-center study, despite Mofid Children's Hospital having specialized rheumatology and clinical immunology wards and being a tertiary, referral center for immunodeficiency disorders, our study was limited by the low number of patients that were eligible to be enrolled in accordance with the established inclusion and exclusion criteria. In addition, the retrospective nature of the study meant that we had to rely on patient medical charts, a few of which were incomplete or had missing data, particularly with regards to confirmatory genetic testing in IEI patients managed by clinical immunologists. Further research, preferably multicenter and prospective studies, will be necessary to verify and expand upon the findings of this study.

Conclusion

Patients with inborn errors of immunity (IEIs) may exhibit autoimmune and rheumatologic manifestations throughout the course of their disease, and such symptoms may even occasionally be the presenting manifestation of an underlying IEI; as such, given that timely diagnosis and early management of IEIs can reduce potential complications and prevent the occurrence or exacerbation of secondary disorders such as rheumatologic diseases, they should be actively sought out and treated in these patients.

Abbreviations

CGD	Chronic Granulomatous Disease
CID	Combined immunodeficiency
CVID	Common Variable Immunodeficiency
ESID	European Society for Immunodeficiencies
FMF	Familial Mediterranean Fever
GPA	granulomatosis with polyangiitis
IBD	Inflammatory Bowel Disease
IEIs	Inborn errors of immunity
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
JIA	Juvenile Idiopathic Arthritis
MCTD	Mixed Connective Tissue Disorder
PAD	Primary Antibody Deficiency
PID	Primary Immunodeficiency Disease
SIgAD	Selective IgA Deficiency
SJIA	Systemic Juvenile Idiopathic Arthritis
SLE	Systemic Lupus Erythematosus
XLA	X-linked Agammaglobulinemia

Acknowledgements

Not applicable.

Author contributions

ZS: literature research and writingSF, MT: data collection and revision, MM, AM, SS, KR, NE, and VJ: acquisition of medical records and clinical data, ZC and RS: study concepts, final revision and guarantor of integrity of the entire study and manuscript editing.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability
All data and analysis are available from the corresponding author on reasonable request.

Declarations

Ethics declarations and consent to participate
In our retrospective study, in line with the Declaration of Helsinki, the need for obtaining informed consent on a case-by-case basis was waivered by the Research Ethics Committee of the School of Medicine - Shahid Beheshti University of Medical Sciences and the study design and methods were approved under the approval ID *IR.SBMU.MSP.REC.1398.434*.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Pediatrics, Division of Allergy and Immunology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Pediatric Respiratory Diseases Research Center (PRDRC), National Research Institute of Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Department of Pediatrics, Division of Pediatric Rheumatology, Shahid Beheshti University of Medical Sciences, Shariati AVE, Hoseinieh Ershad, Mofid Children's Hospital, Tehran 15514 15468, Iran

Received: 26 October 2024 / Accepted: 5 May 2025
Published online: 23 May 2025

References

1. Agarwal S, Mayer L. Diagnosis and treatment of Gastrointestinal disorders in patients with primary immunodeficiency. Clin Gastroenterol Hepatol. 2013;11(9):1050–63.
2. Goyal R, et al. Rheumatologic and autoimmune manifestations of primary immunodeficiency disorders. Curr Opin Rheumatol. 2009;21(1):78.
3. Jesenak M, et al. Pulmonary manifestations of primary immunodeficiency disorders in children. Front Pead. 2014;2:77.
4. Lehman H. Skin manifestations of primary immune deficiency. Clin Rev Allergy Immunol. 2014;46(2):112–9.
5. Seidel MG. Autoimmune and other cytopenias in primary immunodeficiencies: pathomechanisms, novel differential diagnoses, and treatment. Blood. 2014;124(15):2337–44.
6. Tangye SG, et al. Human inborn errors of immunity: 2022 update on the classification from the international union of immunological societies expert committee. J Clin Immunol. 2022;42(7):1473–507.
7. Lewandowicz-Uszyńska A, et al. Primary immunodeficiencies: diseases of children and Adults - A review. Adv Exp Med Biol. 2021;1289:37–54.
8. Bousfiha A, et al. The 2022 update of IUIS phenotypical classification for human inborn errors of immunity. J Clin Immunol. 2022;42(7):1508–20.
9. The French National registry of primary immunodeficiency diseases. Clin Immunol. 2010;135(2):264–72.
10. Kirkpatrick P, Riminton S. Primary immunodeficiency diseases in Australia and new Zealand. J Clin Immunol. 2007;27(5):517–24.
11. Shillitoe B, et al. The united Kingdom primary immune deficiency (UKPID) registry 2012 to 2017. Clin Exp Immunol. 2018;192(3):284–91.
12. Kobrynski L, Powell RW, Bowen S. Prevalence and morbidity of primary immunodeficiency diseases, united States 2001–2007. J Clin Immunol. 2014;34(8):954–61.
13. Yel L. Selective IgA deficiency. J Clin Immunol. 2010;30(1):10–6.
14. Liblau RS, Bach J-F. Selective IgA deficiency and autoimmunity. Int Arch Allergy Immunol. 1992;99(1):16–27.
15. Cassidy JT, Kitson RK, Selby CL. Selective IgA deficiency in children and adults with systemic lupus erythematosus. Lupus. 2007;16(8):647–50.
16. Bussone G, Mouthon L. Autoimmune manifestations in primary immune deficiencies. Autoimmun Rev. 2009;8(4):332–6.
17. Rigby WFC, et al. Increased frequency of complement C4B deficiency in rheumatoid arthritis. Arthr Rhuem. 2012;64(5):1338–44.
18. Sullivan KE. Complement deficiency and autoimmunity. Curr Opin Pediatr. 1998;10(6):600–6.
19. Spârchez M, et al. Primary complement and antibody deficiencies in autoimmune rheumatologic diseases with juvenile onset: a prospective study at two centers. Pediatr Rheumatol. 2015;13(1):51.
20. Dimitriades VR, Sorensen R. Rheumatologic manifestations of primary immunodeficiency diseases. Clin Rheumatol. 2016;35(4):843–50.
21. Chapel H, et al. Primary immune deficiencies–principles of care. Front Immunol. 2014;5:627.
22. Seidel MG, et al. The European society for immunodeficiencies (ESID) registry working definitions for the clinical diagnosis of inborn errors of immunity. J Allergy Clin Immunol Pract. 2019;7(6):1763–70.
23. Goudouris ES. Immunodeficiencies: non-infectious manifestations. J Pediatr (Rio J). 2021;97(Suppl 1):S24–33.
24. Azizi G, et al. Autoimmunity in a cohort of 471 patients with primary antibody deficiencies. Expert Rev Clin Immunol. 2017;13(11):1099–106.
25. Kitcharoensakkul M, Cooper MA. Rheumatologic and autoimmune manifestations in primary immune deficiency. Curr Opin Allergy Clin Immunol. 2019;19(6):545–52.
26. Lim E, et al. Hypogammaglobulinemia in pediatric systemic lupus erythematosus. Lupus. 2013;22(13):1382–7.
27. Padem N et al. Rheumatologic diseases in patients with inborn errors of immunity in the USIDNET registry. Clin Rheumatol. 2022:41.
28. Fischer A, et al. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immunol. 2017;140(5):1388–93.

Publisher's note