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Autoimmune manifestations among 461 patients with monogenic inborn errors of immunity

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Abstract

Background: The inborn errors of immunity (IEIs) are a group of heterogeneous disorders mainly characterized by severe and recurrent infections besides other complications including autoimmune and inflammatory diseases. In this study, we aim to evaluate clinical, immunologic, and molecular data of monogenic IEI patients with and without autoimmune manifestations.

Methods: We have retrospectively screened cases of monogenic IEI in the Iranian PID registry for the occurrence of autoimmunity and immune dysregulation. A questionnaire was filled for all qualified patients with monogenic defects to evaluate demographic, laboratory, clinical, and molecular data.

Results: A total of 461 monogenic IEI patients (290 male and 171 female) with a median (IQR) age of 11.0 (6.0-20.0) years were enrolled in this study. Overall, 331 patients (72.1%) were born to consanguineous parents. At the time of the study, 330 individuals (75.7%) were alive and 106 (24.3%) were deceased. Autoimmunity was reported in 92 (20.0%) patients with a median (IQR) age at autoimmune diagnosis of 4.0 (2.0-7.0) years. Sixteen patients (3.5%) showed autoimmune complications (mostly autoimmune cytopenia) as the first presentation of the disease. Most of the patients with autoimmunity were diagnosed clinically with common variable immunodeficiency (42.4%). The frequency of sinusitis and splenomegaly was significantly higher in patients with autoimmunity than patients without autoimmunity. In patients with autoimmunity, the most common pathogenic variants were identified in *LRBA* (in 21 patients, 23.0%), *ATM* (in 13 patients, 14.0%), and *BTK* (in 9 patients, 10.0%) genes. In the evaluation of autoimmunity by different genes, 4 of 4 *IL10RB* (100%), 3 of 3 *AIRE* (100%), and 21 of 30 *LRBA* (70.0%) mutated genes had the highest prevalence of autoimmunity.

Conclusions: Autoimmune phenomena are common features among patients with monogenic IEI and are associated with a more complicated course of the disease. Therefore, when encountering autoimmune disorders, especially in the setting of dysgammaglobulinemia, it would be appropriate to conduct next-generation sequencing to discover responsible genes for the immune dysregulation at an early stage of the disease.

KEYWORDS
autoimmunity, inborn errors of immunity, inflammation, primary immunodeficiencies

1 | INTRODUCTION

The inborn errors of immunity (IEIs) are a group of heterogeneous disorders mainly characterized by severe and recurrent infections besides other complications including autoimmunity, allergy, lymphoproliferation, and/or malignancy. According to different national registry systems, the distribution and prevalence of IEIs vary among countries, ranging from 4.4/100 000 people in France[1] to 1/1200 people in the United States.[2] Again, based on the compiled data for all national registry reports, monogenic molecular defects in genes worldwide known to cause IEIs were identified in 13.2% of registered IEI patients.[3] Although autoimmunity and immunodeficiency were previously thought to be two ends of a spectrum, an increased understanding of the involved immune regulatory and signaling mechanisms, coupled with the application of genetic analysis, is revealing the complex relationships between IEIs and quality of self-tolerance.[4]

It has been proven that the main mechanisms for autoimmunity in IEIs are defects in the development and/or breakdown of self-tolerance. Generally, defects in T cells and their tolerance induction, defects in B cells and class-switch recombination, and mutation in the genes, which affect the frequency and function of multiple cellular subsets, are the most common defects, which predispose patients with IEIs to autoimmunity. There are several monogenic IEIs in which single rare highly penetrant genetic alterations result in fulminate polyautoimmunity.[5,6] Some of these monogenetic defects in IEI genes including autoimmune regulator (*AIRE*), factor-activated receptor superfamily member 6 (*FAS*), FAS ligand (*FASL*), forkhead box P3 (*FOXP3*), lipopolysaccharide-responsive beige-like anchor protein (*LRBA*), cytotoxic T-lymphocyte–associated protein 4 (*CTLA4*), interleukin-10 (*IL10*), and IL-10 receptors (*IL10R1* and *IL10R2*) are defined by early-onset autoimmunity and/or the occurrence of polyautoimmunity during the course of the disease, while mutations in other genes such as B-cell linker protein (*BLNK*), Bruton tyrosine kinase

Key Message

Autoimmune manifestations are highly observed in patients with inborn errors of immunity (IEI), complicating the clinical course of the disease; therefore, suspicion of disease would be helpful to offer early diagnosis and better prognosis that can be bolstered by next-generation sequencing technology.

(*BTK*), *Janus kinase 3* (*JAK3*), and SH2 domain protein 1A (*SH2DA1*) are associated with lower episodes of autoimmune diseases.[7,8]

In the current study, we aimed to investigate the prevalence and co-occurrence of various types of autoimmune diseases in a large cohort of patients with monogenic IEI and investigated whether clinical and immunologic features, as well as molecular findings of patients, are correlated with the development of autoimmunity.

2 | PATIENTS AND METHODS

2.1 | Patients

A total of 3056 patients with IEI were registered by expert clinical immunologists in the Iranian PID registry (IPIDR) at Children's Medical Center Hospital in Iran,[9] based on updated clinical diagnostic criteria recommended by the European Society for Immunodeficiencies (ESID) Registry Working Party.[10] The putative causative genetic defects were identified in about 33% of registered patients,[9] and among them, patients with monogenic IEIs and available data were selected to be included in this study. Patients with incomplete diagnostic criteria or missed data were excluded. Medical information was collected after obtaining written informed consent from all patients and/or their surrogates. The study was approved by the ethics committee of the Alborz University of Medical Sciences.

2.2 | Data collection

A three-page questionnaire was retrospectively filled by reviewing medical records in the Iranian PID registry (IPIDR) database, and when possible, direct interviews with patients or their parents were performed to collect information regarding demographic data, medical history, physical examination, and laboratory and molecular findings. Demographic data included age, gender, age at disease onset, age of diagnosis, delay of diagnosis, and current life status. Laboratory data composed of complete cell blood count (CBC), T- and B-cell subsets (assessed by flow cytometry analysis), serum levels of immunoglobulins (assessed by nephelometry and enzyme-linked immunosorbent assay [ELISA]), and other advance diagnostic immunologic tests, described previously.[9] For each patient, autoimmune complications before and/or after diagnosis were recorded. The diagnosis of autoimmunity was confirmed by a combination of clinical manifestations and complementary paraclinical findings including pathologic results of the biopsy taken directly or through endoscopy and/or colonoscopy, laboratory tests (direct coombs test, antinuclear antibody [ANA] profile, fluorescent antinuclear antibody [FANA] test, anti–double-stranded DNA [anti-dsDNA], and other specific autoantibodies), and radiologic studies based on international criteria.[11] The evaluation for autoimmunity diagnosis was reviewed for all patients by an immunologist and a subspecialist related to the affected organ.[12] The presence of more than one autoimmune disease in a single patient was defined as polyautoimmunity.[13]

2.3 | Mutation analysis

Whole peripheral blood samples were taken, and genomic DNA extraction was performed for the study population. For patients with classical clinical presentations suggestive of a specific IEI, the Sanger sequencing was performed on the most likely genes. For patients in whom the Sanger sequencing failed or who had a clinical presentation resembling several genetic defects (phenocopies), whole-exome sequencing was performed and analyzed as previously described.[9,14-16] The pathogenicity of all disease-attributable gene variants was reevaluated using the updated guideline for interpretation of molecular sequencing by the American College of Medical Genetics and Genomics (ACMG).[17]

2.4 | Statistical analysis

Values were presented as frequency (number and percentage), mean ± standard deviation (SD), and median (interquartile range, IQR), as appropriate. Fisher's exact tests and chi-square tests were used for 2 × 2 comparisons of categorical variables. To compare numerical variables, for non-parametric data Mann-Whitney *U* test and the Kruskal-Wallis test and for parametric data t tests and one-way analysis of variance (ANOVA) were used. The Shapiro-Wilk test was carried out to assume the normality for a variable, and the parametric or non-parametric tests were done accordingly. Statistical analyses were performed using the SPSS software package, version 26 (SPSS Inc). A *P*-value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline demographic data

A total of 461 monogenic IEI patients (171 female; 37.1%) with a median (IQR) age of 11.0 (6.0-20.0) years were enrolled in this study. The median (IQR) age at onset, age at IEI diagnosis, and diagnostic delay were 0.9 (0.2-2.0), 4.0 (1.0-7.0), and 2.0 (0.2-5.0) years, respectively. Overall, 331 patients (72.1%) were born to consanguineous parents. At the time of the study, 25 individuals (5.3%) were dropped from follow-up and 106 patients (24.3%) were deceased. The mean follow-up for survived cases was 14.1 (±10.49) years. The patients' characteristics are summarized in Table 1.

Autoimmunity was reported in 92 (20.0%, 28 of which with polyautoimmunity) patients with median (IQR) age at autoimmune diagnosis of 4.0 (2.0-7.0) years. The median (IQR) age at the time of the study (13 [8-21.5] vs. 11 [5.7-20] years, $P = .030$), age at onset of symptoms (1 [0.5-3] vs. 0.8 [0.2-2.0], $P = .006$), and age at

TABLE 1 Demographic data in patients with monogenic inborn errors of immunity

Parameters	Total (n = 461)	With autoimmunity (n = 92)	Without autoimmunity (n = 369)	#P-value	Mono-autoimmunity (n = 64)	Polyautoimmunity (n = 28)	#P-value
Sex ratio, M/F (n = 461)	290/171	53/39	237/132	.240	41/23	12/16	.058
Age, y, median (IQR) (n = 451)	11 (6-20)	13 (8-21.5)	11 (5.7-20)	**.030***	11 (6.5-21.5)	14.5 (10.2-21.5)	.307
Age at onset, y, median (IQR) (n = 449)	0.9 (0.2-2)	1 (0.5-3)	0.8 (0.2-2)	**.006***	1 (0.5-3)	1.5 (0.3-2.7)	.893
Age at diagnosis of IEI, y, median (IQR) (n = 438)	4 (1-7)	5 (3-8.7)	3 (1-7)	**.001***	5 (1-8)	6 (4-9.7)	.278
Delay in diagnosis, y, median (IQR) (n = 435)	2 (0.2-5)	2.5 (0.2-5)	1.5 (0.2-4.5)	.404	2 (0-4.1)	3.7 (2-5.9)	**.010***
Course of disease, y, median (IQR) (n = 445)	8.7 (3.8-16.3)	10 (5.5-18)	8 (3.2-16)	.054	9 (4.5-18)	11 (7.3-19.7)	.132
Age at diagnosis of autoimmunity, y, median (IQR) (n = 95)	4 (2-7)	3.5 (2-6.6)	4 (2-7.5)	.514	3 (2-6.9)	4 (2.4-5.5)	.510
Consanguinity (%) (n = 459)	331 (72.1%)	64 (71.1%)	267 (72.4%)	.813	41 (66.1%)	23 (82.1%)	.121
Dead/alive ratio** (n = 436)	106/330	18/67	88/263	.453	11/46	7/21	.545

Note: The median is shown [with interquartile range IQR: 25th and 75th percentiles].

Abbreviations: F, female; IEIs; inborn errors of immunity; M, male; Y, year.

* and bold values indicate $P < .05$ and are considered significant significant.

**Alive/dead data are not available for 7 patients.

#*P*-value for comparison of patients with and without autoimmunity.

##*P*-value for comparison of patients with mono-autoimmunity and polyautoimmunity.

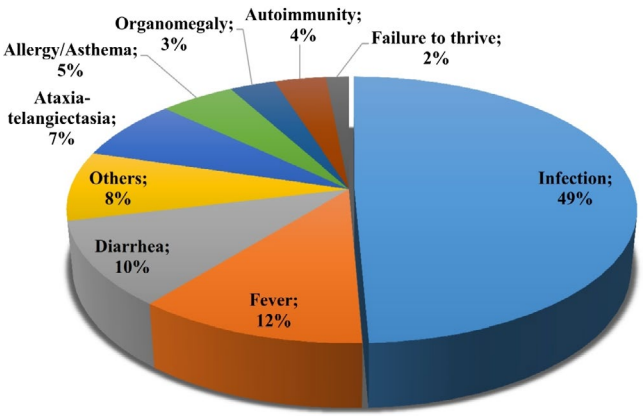

FIGURE 1 First presentation in patients with monogenic inborn errors of immunity

the time of diagnosis (5 [3.0-8.7] vs. 3 [1-7], $P = .001$) were higher in patients with autoimmunity compared to monogenic patients without autoimmunity. The median (IQR) diagnostic delay in patients with polyautoimmunity was higher than that in patients with mono-autoimmunity (3.7 [2-5.9] vs. 2.0 [0-4.1], $P = .010$). When patients split based on mutated genes, there were no significant differences regarding the mentioned ages between ATM-deficient patients with and without autoimmunity. Similar results were observed in BTK- and LRBA-deficient patients (Table S1).

3.2 | Clinical evaluation

As shown in Figure 1, the most prevalent first presentation of immunodeficiency in all IEI patients was an infectious disease (n = 225, 49.0%). Of note, 16 patients (3.5%) showed autoimmune complications (mostly autoimmune cytopenia) as the first presentation of the disease. In 48.4% of patients with autoimmunity, the diagnosis of autoimmune disorders preceded the diagnosis of IEI, while in 39.6% of patients, autoimmune complications were identified later during the course of the disease. Most of the monogenic patients with autoimmunity were clinically diagnosed with common variable immunodeficiency (CVID) (42.4%), hyper-IgM (HIgM) syndrome (13.0%), and agammaglobulinemia (12.0%) (Figure 2 and Figure S1).

Among patients with autoimmunity, hematologic (42.2%), rheumatologic (26.7%), gastrointestinal (27.2%), dermatologic (16.7%), neurologic (7.8%), and endocrine (7.8%) affected organs by autoimmune diseases were documented. Moreover, in patients with monogenic IEIs, immune thrombocytopenic purpura (ITP) (6.5%), juvenile idiopathic arthritis (JIA) (4.8%), and autoimmune

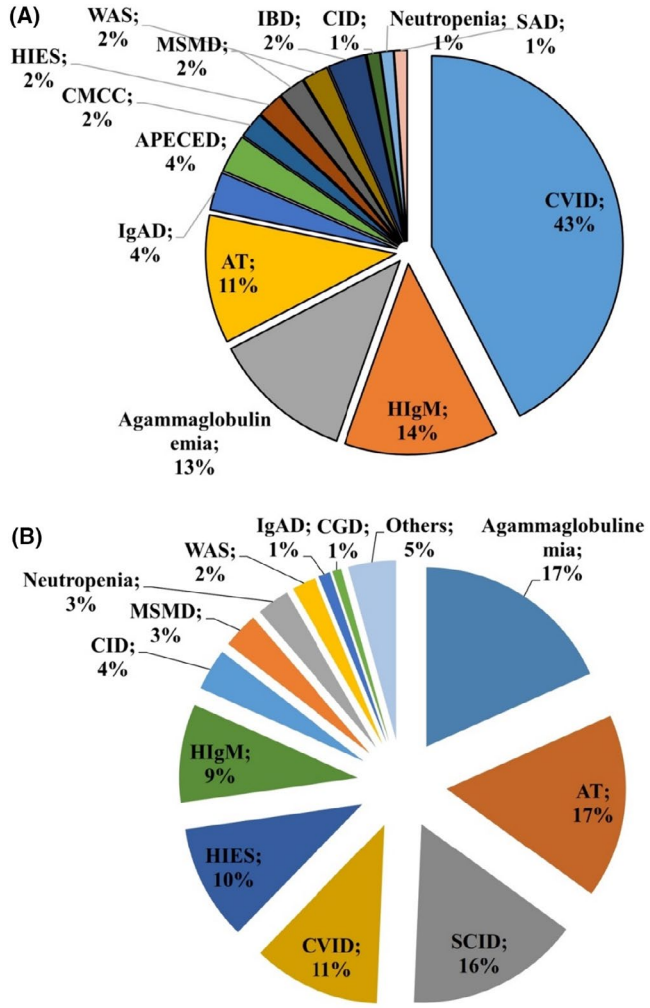

FIGURE 2 The spectrum of clinical diagnoses in patients with autoimmunity (A) and without autoimmunity (B). CVID, common variable immunodeficiency; IBD, inflammatory bowel disease; WHIM, wart hypogammaglobulinemia infections and myelokathexis; HIgM, hyper-IgM syndrome; HIES, hyper-IgE syndrome; CGD, chronic granulomatous disease; MSMDs, Mendelian susceptibility to mycobacterial diseases; IgAD, IgA deficiency; WAS, Wiskott-Aldrich syndrome; AT, ataxia-telangiectasia; SCID, severe combined immunodeficiency; SAD, specific antibody deficiency; CID, combined immunodeficiency; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

hemolytic anemia (AIHA) (3.9%) were the most reported autoimmune disorders (Table 2 and Figure S2). While the most frequent autoimmune diseases in patients with *LRBA* or *ATM* mutations were ITP (36.7% and 7.8%, respectively), inflammatory bowel disease (IBD) (100%) was reported in all four patients with a mutation in the *IL10RB* gene. As the most frequent autoimmune diseases, autoimmune thyroiditis, Addison disease, and autoimmune alopecia were reported in two of three patients with mutations in the *ARIE* gene.

In 28 patients with polyautoimmunity, 19 patients (67.8%) had two types, four patients (14.3%) had three types, and five patients (17.8%) had four types of autoimmunities. As shown in Figure 3, the most common overlapping phenotypes were the combination of autoimmune cytopenia and autoimmune enteropathy in five (17.9%) patients and then autoimmune rheumatologic disorder and autoimmune enteropathy in four (14.3%) patients with polyautoimmunity.

The clinical manifestations of patients with monogenic IEIs are presented in Table 3. The infectious complication was reported in more than 80% of monogenic IEIs. The frequency of otitis media, sinusitis, candidiasis, septicemia, septic arthritis, bronchiectasis, splenomegaly, hepatomegaly, clubbing, enteropathy, and allergy and asthma was significantly higher in patients with autoimmunity than patients without autoimmunity. The frequency of candidiasis, hepatomegaly, enteropathy, and allergy and asthma was significantly higher in patients with polyautoimmunity than those with mono-autoimmunity.

3.3 | Immunologic evaluation

The summary of immunologic findings is represented in Table 4. Lymphocyte count in 42.7% (177 of 415 patients with available data) was within the normal range, and lymphopenia was reported in 16.4% (68 of 415) patients. Most of the patients had normal lymphocyte subsets including $CD3^+$ (54.4% [212 of 390]), $CD4^+$ (56.5% [218 of 386]), $CD8^+$ (53.5% [205 of 383]), $CD19^+$ (38.5% [146 of 379]), and $CD16^+56^+$ (60.4% [110 of 182]). Although in the majority of IEI patients NK cells were within the normal range, patients without autoimmunity had a higher frequency of $CD16^+/56^+$ NK cells than patients with autoimmunity.

Similarly, the frequency of patients with $CD16^+56^+$ NK cell lymphopenia (based on the adjusted age-matched normal range) was reported to be higher in patients with autoimmunity than patients without autoimmunity (24.4% vs. 11.7%), while fewer patients with $CD3^+$ (10.8% vs. 16.3%), $CD4^+$ T-cell (32.5% vs. 41.8%), $CD8^+$ T-cell (8.9% vs. 14.5%), and $CD19^+$ B-cell (44.2% vs. 46.7%) lymphopenia were reported in autoimmunity group compared to patients without autoimmunity. The frequency of patients with low serum levels of IgG (66.7% vs. 54.5%), IgA (62.4% vs. 59.7%), and IgM (43.0% vs. 37.4%) was reported to be higher in patients with autoimmunity than patients without autoimmunity. Although the serum level of IgE was within the normal range in about 286 patients (76.1% [286 of 376]), patients without autoimmunity had a higher serum level of IgE (5.0 [1.0-65.5] vs. 1.5 [0.0-10.1] IU/mL, $P = .004$) compared to patients with autoimmunity. In this study, the highest number of included monogenic IEI patients belonged to the *ATM*, *BTK*, and *LRBA* gene defects (77, 69, and 30 patients, respectively). The comparison of epidemiologic and immunologic findings in *ATM* (as a representative of combined immunodeficiency group), *BTK* (as a representative of predominantly antibody deficiency group), and *LRBA* (as a representative of immune dysregulation group) patients with and without autoimmunity is presented in Table S1. The *ATM* mutated patients with autoimmunity had a lower serum level of IgG and a higher level of IgM in comparison with patients without autoimmunity ($P < .001$ and $P = .038$, respectively).

TABLE 2 Autoimmune manifestations in patients with mono-autoimmunity and polyautoimmunity

Parameters	Total (n = 461)	Mono-autoimmunity (n = 64)	Polyautoimmunity (n = 28)	*P*-value
Immune thrombocytopenic purpura	30 (6.5%)	16 (25.8%)	14 (50%)	**.024***
Autoimmune hemolytic anemia	18 (3.9%)	5 (8.1%)	13 (46.4%)	**<.001***
Autoimmune enteropathy	4 (0.9%)	1 (1.6%)	3 (10.7%)	.088
Rheumatoid arthritis/juvenile idiopathic arthritis	22 (4.8%)	12 (19.4%)	10 (35.7%)	.095
Autoimmune thyroiditis	6 (1.3%)	0 (0%)	6 (21.4%)	**.001***
Vitiligo	5 (1.1%)	3 (4.8%)	2 (7.1%)	.645
Insulin-dependent diabetes mellitus	2 (0.4%)	2 (3.2%)	0 (0.0%)	1.0
Autoimmune Addison disease	2 (0.4%)	0 (0%)	2 (7.1%)	.094
Celiac disease	5 (1.1%)	3 (4.8%)	2 (7.1%)	.645
Guillain-Barré syndrome	4 (0.9%)	4 (6.5%)	0 (0%)	.306
Alopecia areata	6 (1.3%)	3 (4.8%)	3 (10.7%)	.370
Inflammatory bowel disease	13 (2.8%)	7 (10.9%)	6 (21.4%)	.090
Myasthenia gravis	1 (0.2%)	0 (0%)	1 (3.6%)	.311
Systemic lupus erythematous	3 (0.7%)	1 (1.6%)	2 (7.1%)	.227
Psoriasis	4 (0.9%)	3 (4.8%)	1 (3.6%)	1.0
Kawasaki disease	2 (0.4%)	1 (1.6%)	1 (3.6%)	.528
Evans syndrome	1 (0.2%)	0 (0%)	1 (3.6%)	.311
Multiple sclerosis	1 (0.2%)	0 (0%)	1 (3.6%)	.311
Autoimmune hepatitis	4 (0.9%)	3 (4.8%)	1 (3.6%)	1.0

* and bold values indicate $P < .05$ and are considered significant significant.

3.4 | Molecular findings

Among patients without autoimmunity, the most commonly identified pathogenic variants were *ATM* in 64 patients (17.1%), *BTK* in 60 patients (16.0%), *DOCK8* in 24 patients (6.4%), *CD40L* in 21 patients (5.6%), and *STAT3* in 17 patients (4.5%). In patients with autoimmunity, the most common pathogenic variants included *LRBA* in 21 patients (23.0%), *ATM* in 13 patients (14.0%), and *BTK* in 9 patients (10.0%). In the evaluation of autoimmunity phenotype with a specific genetic defect, 4 of 4 *IL10RB* (50.0%), 3 of 3 *AIRE* (100.0%), and 21 of 30 *LRBA* (70.0%) mutated genes had the highest prevalence of autoimmunity. In patients with polyautoimmunity, the most commonly identified pathogenic variants were *LRBA* in 11 patients (39.0%), *ATM* in 3 patients (10.7%), and *AIRE* in 2 patients (7.0%). In the evaluation of polyautoimmunity by different genetic defects, 2 of 3 *AIRE* (66.0%) and 11 of 21 *LRBA* (52.0%) mutated genes were associated with the highest prevalence of polyautoimmunity. One patient for each of the genes *CD25*, *FOXP3*, *MVK*, and *DCLRE1C* was presented with polyautoimmunity in this cohort of patients (Table S2).

4 | DISCUSSION

In the last decade, the list of monogenic immune defects with organ-specific autoimmunity, as the major component of the disease, is rapidly expanding. In this regard, we retrospectively investigated autoimmune manifestations in a cohort of monogenic IEI patients and compared clinical, immunologic, and molecular characteristics between patients with and without autoimmunity. Although autoimmunity is a very well-known entity in IEI, there is no enough detailed study in the literature that compares patients with/without autoimmunities in one unique gene defect. The current research is a comprehensive study in this area, so its novelty is aiming to answer this question in a large cohort.

In the current study, the age at the time of the study, at the onset of IEI, and the diagnosis were significantly higher in patients with autoimmunity compared with others. In addition, the number of autoimmune disorders was associated with a greater delay in the diagnosis of underlying IEIs. A recent study also reported a considerably longer diagnosis delay in IEI patients with autoimmunity and related this to the less severe non-infectious presentations, which had probably hindered early screening of IEIs.[18] However, this may not be the reason in our study since patients with autoimmunity had a more complex disorder with higher rates of infections, candidiasis, organomegaly, enteropathy, and atopy. Instead, this may imply overlooking of autoimmune manifestations as a sign of immunodeficiency by physicians who may not yet be familiar with the heterogeneous clinical picture and appropriate diagnostic approach to these disorders and lack of multidisciplinary investigation of these patients. Therefore, as in previous studies,[8,19] we suggest adding autoimmunity to the warning signs of inborn errors of immunity, thereby emphasizing the important diagnostic and prognostic role of autoimmune disorders.

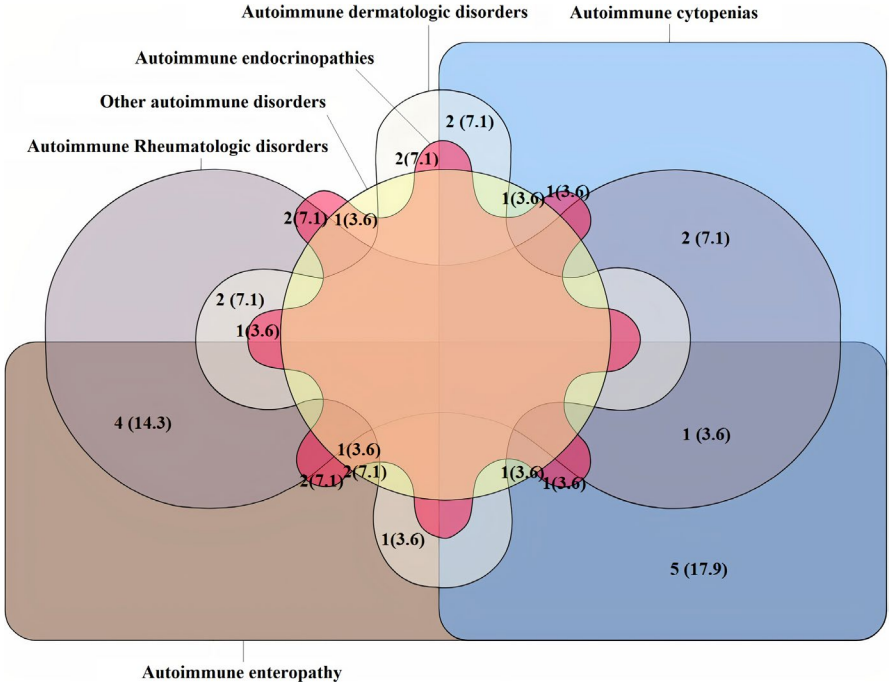

FIGURE 3 The frequency (percentage) for the overlap between different types of autoimmune disorders is illustrated. The most common overlap syndrome in patients with polyautoimmunity was the combination of hematologic and gastrointestinal autoimmune disorders

TABLE 3 Clinical manifestations in patients with monogenic inborn errors of immunity

Parameters	Total (n = 461)	With autoimmunity (n = 92)	Without autoimmunity (n = 369)	#*P*-value	Mono-autoimmunity (n = 64)	Polyautoimmunity (n = 28)	#*P*-value
Infectious manifestation, n (%)	376 (81.7%)	78 (86.7%)	298 (80.5%)	.286	53 (85.5%)	25 (89.3%)	.747
Otitis media, n (%)	156 (33.9%)	42 (46.7%)	114 (30.8%)	**.002***	25 (40.3%)	17 (60.7%)	.073
Sinusitis, n (%)	117 (25.4%)	38 (42.2%)	79 (21.4%)	**<.001***	22 (35.5%)	16 (57.1%)	.054
Pneumonia, n (%)	230 (50%)	52 (57.8%)	178 (48.1%)	.051	33 (53.2%)	19 (67.9%)	.193
Skin infection, n (%)	91 (19.8%)	13 (14.4%)	78 (21.1%)	.822	7 (11.3%)	6 (21.4%)	.214
Candidiasis, n (%)	65 (14.1%)	20 (22.2%)	45 (12.2%)	**.003***	10 (16.1%)	10 (35.7%)	**.039***
Conjunctivitis, n (%)	50 (10.9%)	14 (15.6%)	36 (9.7%)	.106	8 (12.9%)	6 (21.4%)	.352
Meningitis, n (%)	36 (7.8%)	10 (11.1%)	26 (7%)	.473	7 (11.3%)	3 (10.7%)	1.0
Septicemia, n (%)	9 (2%)	5 (5.6%)	4 (1.1%)	**.013***	2 (3.2%)	3 (10.7%)	.172
Septic arthritis, n (%)	12 (2.6%)	7 (7.8%)	5 (1.4%)	**.004***	3 (4.8%)	4 (14.3%)	.198
Bronchiectasis, n (%)	59 (12.8%)	19 (21.1%)	40 (10.8%)	**.005***	10 (15.6%)	9 (32.1%)	.085
Neutropenia, n (%)	51 (11.1%)	9 (10%)	42 (11.4%)	.756	7 (11.3%)	2 (7.1%)	.715
Failure to thrive, n (%)	87 (18.9%)	18 (20%)	69 (18.6%)	.883	13 (21%)	5 (17.9%)	.733
Splenomegaly, n (%)	80 (17.4%)	36 (40%)	44 (11.9%)	**<.001***	22 (35.5%)	14 (50%)	.193
Hepatomegaly, n (%)	80 (17.4%)	27 (30%)	53 (14.3%)	**<.001***	14 (22.6%)	13 (46.4%)	**.022***
Lymphadenopathy, n (%)	74 (16.1%)	22 (22.4%)	52 (14.1%)	.105	14 (22.6%)	8 (28.6%)	.540
Clubbing, n (%)	39 (8.5%)	14 (15.6%)	25 (6.8%)	**.006***	7 (11.3%)	7 (25%)	.120
Malignancy, n (%)	11 (2.4%)	4 (4.4%)	7 (1.9%)	.503	3 (4.8%)	1 (3.6%)	1.0
Enteropathy, n (%)	107 (23.4%)	36 (40.4%)	71 (19.2%)	**<.001***	19 (31.1%)	17 (60.7%)	**.008***
Allergy/asthma, n (%)	56 (12.2%)	17 (18.9%)	39 (10.6%)	**.001***	7 (11.3%)	10 (35.7%)	**.006***

* and bold values indicate $P < .05$ and are considered significant significant.

#*P*-value for comparison of patients with and without autoimmunity.

##*P*-value for comparison of patients with mono-autoimmunity and polyautoimmunity.

TABLE 4 Immunologic profile in patients with monogenic inborn errors of immunity

Parameters; median (IQR)	Total (n = 461)	With autoimmunity (n = 92)	Without autoimmunity (n = 369)	#*P*-value	Mono-autoimmunity (n = 64)	Polyautoimmunity (n = 28)	#*P*-value
WBC × 10^3 (cell/μL), (n = 420)	8.0 (5.5-11.9)	7.17 (5.19-10.6)	8.3 (5.64-12.03)	.057	7.17 (5.08-11.95)	7.0 (5.017-9.097)	.666
Hemoglobin (g/dL) (n = 382)	11 (10-12.7)	11 (10-13)	11 (10-12.4)	.527	11 (10-13)	12 (10-13)	.487
Absolute lymphocyte counts (cells /μL), (n = 415)	2772 (1649-4876)	2535 (1653-4512)	2779.5 (1634-5147.2)	.422	2800 (1651-4365)	2263 (1555-4581)	.626
Absolute neutrophil counts (cells /μL) (n = 388)	3472 (2033-5988)	3041.5 (1804.5-6024)	3581.5 (2119.5-5369.2)	.195	3172 (1565-5443)	2989 (1883-5472)	.862
$CD3^+$ T cells (% of lymphocytes) (n = 395)	67 (49.7-82)	68.5 (55.7-79)	66.9 (47.5-82)	.520	67 (56.2-78.7)	72.5 (52.2-84.7)	.492
$CD4^+$ T cells (% of T cells) (n = 395)	32 (19-43)	32.8 (23-42)	32 (16.8-44)	.210	34.5 (24.5-42)	31.5 (21-41.6)	.443
$CD8^+$ T cells (% of T cells) (n = 388)	27 (18-39)	26.5 (19-37)	27 (17-39.9)	.860	27 (18.5-36.5)	26 (19.3-39.5)	.830
$CD16^+56^+$ NK cells (% of lymphocytes) (n = 186)	9 (4-19)	5.5 (2.7-11.3)	10 (5-27)	**.005***	6 (2.6-17.1)	3 (2-9.5)	.495
$CD19^+$ B cells (% of lymphocytes) (n = 389)	8 (1-20)	8 (2-20.7)	8 (0.6-20)	.326	8.2 (2-21)	7.5 (2.4-21.5)	.955
IgG (mg/dL) (n = 434)	377 (99.7-876.2)	320 (105.5-619.5)	426 (99-908)	.132	310 (111-622)	340 (41.5-640)	.587
IgA (mg/dL) (n = 432)	13 (3-67.7)	9.5 (2-50.2)	14 (3-74.1)	.125	8 (0.7-41.7)	14.9 (3.5-67.7)	.272
IgM, mg/dL (n = 434)	65 (19-160.7)	50 (19.5-153)	72 (19-164)	.583	49 (20-159)	58 (18-141.2)	.797
IgE (IU/mL) (n = 378)	5 (1-50)	1.5 (0-10.1)	5 (1-65.5)	**.004***	2.5 (1-14.7)	0.5 (0-7.1)	**.033***

Note: The median is shown with 25th and 75th percentiles.

Abbreviations: Hb, hemoglobin; Ig, immunoglobulin; NK cell, natural killer cell; WBC, white blood cell.

* and bold values indicate $P < .05$ and are considered significant significant.

#*P*-value for comparison of patients with and without autoimmunity.

##*P*-value for comparison of patients with mono-autoimmunity and polyautoimmunity.

The prevalence of polyautoimmunity and the number of autoimmunities per individual in patients with IEIs are not clear; however, several recent studies [18-20] have partly addressed these uncertainties. In the present study, among 92 patients with autoimmune disorders, 64 (69.6%) patients had a single type of autoimmunity, 19 (20.6%) patients had two, 4 (4.3%) patients had three, and 5 (5.4%) patients had four types of autoimmunities. Although the total percentage of patients with autoimmunity is similar to the Kuwait report with a high level of parental consanguinity and geographical proximity (19.9%),[18] which also reported few numbers of patients, the percentages concerning numbers of autoimmunities per individual are somewhat like that reported in the French cohort.[20] However, more studies on autoimmune disorders in IEI patients are needed to draw a comprehensive pattern of autoimmune disorders.

In the whole IEI patients and patients with autoimmunity, the most common autoimmune complication was of the hematologic type that included ITP and AIHA, especially in patients with LRBA deficiency.[11,21-24] This is in accordance with studies from other countries, namely Turkey,[19] France,[20] Mexico,[25] and Austria,[26] which found autoimmune cytopenias to be the most common autoimmune manifestations among patients with IEIs. However, other studies from the Slovenian[27] and United States Immunodeficiency Network (USIDNET)[28] registries reported autoimmune enteropathy as the most common autoimmune manifestation and another study from Turkish patients reported IBD and IBD-like as the most frequent autoimmunity.[29] Intriguingly, we observed the most overlap between autoimmune cytopenia and autoimmune enteropathy. These reports emphasize the undeniable effect of epigenetic and environmental factors in autoimmune manifestations, but more importantly introduce autoimmune cytopenia as a presentation that should be evaluated for a second autoimmune disorder, particularly in the gastrointestinal system, and careful follow-up for an underlying immunodeficiency.[30]

The autoimmune cytopenia in CVID has a prevalence of 10.2%-40.0%,[31-33] estimated to be 702.9 times higher than that in the general population.[34] Notably, we found a higher frequency of splenomegaly, hepatomegaly, and enteropathy among CVID patients with autoimmune cytopenia. It is in line with previous studies from the USIDNET and ESID registries, which reported a strong correlation between lymphoproliferation, enteropathy, and autoimmune cytopenia in this IEI entity.[32,35] Therefore, autoimmune cytopenia may be a predicting factor for a more complex course of the disease, highlighting the need for monitoring the progression of non-infectious complications.[32]

In this cohort, autoimmunity was correlated with the absolute number of NK cells. NK cell subsets (mostly CD56 bright) have immune regulatory roles mediated by secretion of cytokines and chemokines and killing antigen-presenting cells (APCs) or overactivated T cells,[36,37] particularly in the gut and liver.[38] We also observed a negative correlation between NK cell frequency and the presence of either autoimmune enteropathy or hepatitis. However, further studies are required to elucidate the role of NK cells in organ-specific autoimmune pathomechanisms, which can lead to the introduction of novel targeted therapy for the gut and liver autoimmune/inflammatory disorders. Most of the patients with autoimmunity had a clinical diagnosis of CVID, and the most common mutated gene identified in patients with mono- and polyautoimmunity was *LRBA*. It seems in patients with CVID phenotype and predominant autoimmune manifestations, a search for the main gene panel involved in the immune regulation would be beneficial.

One of the limitations of the current study is that the studied patients belong to a heterogeneous group of disorders with different immunologic characteristics. For example, CD3 count is expected to be low in patients with SCID or AT, but normal in patients with BTK deficiency, the same may apply for serum immunoglobulins level, which is low in CVID but normal in other IEIs such as severe congenital neutropenia or STAT3 deficiency. Therefore, the future study should include patients affected by a single genetic defect and an appropriate sample size analyzing specific monogenic defects.

In conclusion, autoimmune phenomena are common features among Iranian patients with IEI and are associated with a more complicated course of the disease. Therefore, when encountering autoimmune disorders especially in the setting of dysgammaglobulinemia, it would be appropriate to set up a plan for careful follow-up of the patient and (where applicable) search for the mutated genes that may have been responsible for the immune dysregulation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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