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Monogenic Primary Immunodeficiency Disorder Associated with Common Variable Immunodeficiency and Autoimmunity

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Keywords
Primary immunodeficiency · Common variable immunodeficiency · Autoimmunity · Sanger sequencing · Whole-exome sequencing

Abstract
Background: Common variable immunodeficiency (CVID) is the most frequent primary immunodeficiency disorder mainly characterized by recurrent bacterial infections besides other immunological defects including loss of or dysfunction of B cells and decreased immunoglobulin levels. In this study, our aim is to evaluate clinical, immunological, and molecular data of patients with a primary clinical diagnosis of CVID and autoimmune phenotype with a confirmed genetic diagnosis. ***Methods:*** Among 297 patients with CVID, who were registered in the Iranian Primary Immunodeficiency Registry at Children's Medical Center Hospital in Iran, 83 patients have been genetically examined and 27 patients with autoimmunity and confirmed genetic mutations were selected for analysis. Whole-exome sequencing and confirmatory Sanger sequencing methods were used for the study population. A questionnaire was retrospectively filled for all patients to evaluate demographic, laboratory, clinical, and genetic data. ***Results:*** In the 27 studied patients, 11 different genetic defects were identified, and the most common mutated gene was *LRBA*, reported in 17 (63.0%) patients. Two patients (7.7%) showed autoimmune complications as the first presentation of immunodeficiency. Eleven patients (40.7%) developed one type of autoimmunity, and 16 patients (59.3%) progressed to poly-autoimmunity. Most of the patients with mono-autoimmunity (n = 9, 90.0%) primarily developed infectious complications, while in patients with poly-autoimmunity, the most common first presentation was enteropathy (n = 6, 37.6%). In 13 patients (61.9%), the diagnosis of autoimmune disorders preceded the diagnosis of primary immunodeficiency. The most frequent autoimmune manifestations were hematologic (40.7%), gastrointestinal (48.1%), rheumatologic (25.9%), and dermatologic (22.2%) disorders. Patients with poly-autoimmunity had lower regulatory T cells than patients with mono-autoimmunity. ***Conclusion:*** In our cohort, the diagnosis of autoimmune disorders preceded the diagnosis of primary immunodeficiency in most patients. This association highlights the fact that patients referring with autoimmune manifestations should be evaluated for humoral immunity.

Introduction

Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency mainly characterized by recurrent bacterial infections and immune dysregulation. The distribution and prevalence of CVID vary between countries. It ranges from 1 in 50,000 to 1 in 25,000 people in European populations and less frequent in African and East Asian populations [1, 2]. Over the past years, quality of life and prognosis for patients with CVID have significantly increased due to advances in the management and prophylaxis of infection, such as immunoglobulin (Ig) replacement and antimicrobial agents which are now highly effective at preventing and treating infections in many CVID [3]. Having improved in the management of infection, autoimmunity is becoming an increasing cause of morbidity and mortality [3].

Although CVID is the diagnosis of exclusion, its clinical diagnosis may mimic by several genetic defects that affect different components of the innate and adaptive responses associated with autoimmune disorders [4]. Different mechanisms have been proposed for autoimmunity as one of the main complications of CVID; however, some monogenetic defects, including transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI, *TNFRSF13B*) deficiency, inducible T-cell costimulator (*ICOS*) deficiency, B-cell activating factor receptor (BAFF-R, *TNFRSF13C*) deficiency, mutations in molecules involved in the activation of B-cell receptor (*CD19*, *CD20*, *CD21*, and *CD81*), and lipopolysaccharide-responsive beige-like anchor protein (*LRBA*) deficiency may predispose patients to autoimmunity and immune dysregulation [5]. Although autoimmunity and immunodeficiency were previously thought to be two ends of a spectrum, an increased understanding of the complex immune regulatory and signaling mechanisms involved, coupled with the application of genetic analysis, is revealing the complex association of some specific genes underlying CVID with autoimmune phenotype [6]. Many autoimmune manifestations are prevalent in CVID cohorts across a range of monogenic forms of CVID [3]. Autoimmunity is present in 20–30% of CVID patients [5, 7]. The 2 most prominent autoimmunities in CVID are idiopathic thrombocytopenic purpura (ITP) (10–12%) and autoimmune hemolytic anemia (AIHA) (5–7%), which are commonly correlated with splenomegaly [5, 7]. Occasionally, the onset of autoimmune cytopenia is earlier than the diagnosis of CVID, so the differential diagnosis of humoral immunodeficiency with adult onset should be considered by hematologists [7]. Autoimmune cytopenias associated with CVID have some immunological indicators including low numbers of class-switched memory B cells, expanded $CD21^{low}$ B cells, and low numbers of regulatory T cells (Tregs). Other autoimmunities including vitiligo, thyroid disorders, psoriasis, pernicious anemia, systemic lupus erythematosus, and rheumatoid arthritis (RA) have been reported in CVID patients [5]. In this study, our aim is to evaluate clinical, immunological, and molecular data of monogenic patients with a clinical diagnosis of CVID and autoimmune phenotype.

Patients and Methods

Patients

A total of 297 patients with CVID were registered by expert clinical immunologists in the Iranian Primary Immunodeficiency Registry (IPIDR) at Children's Medical Center Hospital in Iran [8] on the basis of updated diagnostic criteria recommended by the European Society for Immunodeficiencies (ESID) [9]. Among 83 registered patients with an initial diagnosis of CVID with known gene mutations, a total of 27 patients with autoimmunity and confirmed genetic mutations were selected for analysis [10, 11]. The study was approved by the Ethics Committee of the National Institute for Medical Research Development.

Mutation Analysis

Whole peripheral blood samples were taken from our study population, and genomic DNA extraction was performed for the available patients with a tentative diagnosis of CVID and autoimmune phenotype. The whole-exome sequencing and confirmatory Sanger sequencing methods were carried out according to a pipeline published previously [10, 11]. The pathogenicity of all disease-attributable gene variants was re-evaluated using the updated guideline for interpretation of molecular sequencing by the American College of Medical Genetics and Genomics (ACMG) [12].

Data Collection

A questionnaire was retrospectively filled by reviewing medical records and the IPIDR database for those patients with a confirmed molecular diagnosis, and if possible, data were updated by direct interviews of these selected patients to collect information including demographic data, clinical manifestations, medical history, physical examination, laboratory and molecular findings, and mortality. We investigated demographic data such as age, gender, age at disease onset, age at diagnosis, and delay of diagnosis. Laboratory data were recorded including complete cell blood count, T-cell and B-cell subsets (was assessed using flow cytometry analysis), serum levels of immunoglobulins (was assessed using nephelometry and enzyme-linked immunosorbent assay), and autoantibodies as described previously [10, 13]. For each patient, autoimmune complication before and/or after diagnosis was recorded. The diagnosis of autoimmunity was confirmed by a combination of clinical manifestations and complementary paraclinical findings including the pathology results of the biopsy taken over endoscopy and/or colonoscopy and radiologic studies based on international criteria. The evaluation for autoimmunity diagnosis was reviewed for all patients by an immunologist and a subspecialist related to the affected organ as explained previously [14]. 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.

Statistical Analysis

Values were presented as frequency (number and percentage), mean ± SD, and median (interquartile range, IQR), as appropriate. Fisher's exact test and χ^2 tests were used for 2×2 comparisons of categorical variables. To compare numerical variables, the Mann-Whitney U test was used for nonparametric data and *t* tests were used for parametric data. The Shapiro-Wilk test was used to check the assumption of normality for a variable, and the parametric or nonparametric tests were carried out according to the normality assumption. Statistical analyses were performed using the SPSS software package, version 22 (SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant.

Table 1. Demographic data on patients with poly-autoimmunity and mono-autoimmunity

Parameters	Total	Mono-autoimmunity	Poly-autoimmunity	*p* value
Patients, *n*	27	11	16	–
Sex ratio (M/F), *n*	11/16	6/5	5/11	0.26
Age, years	17 (11.0–22.0)	17.0 (6.0–24.0)	18.5 (12.25–21.5)	0.52
Age at onset, years	2.0 (0.6–3.0)	1.25 (0.5–2.25)	2.0 (0.6–4.0)	0.52
Age at diagnosis, years	7.0 (3.75–12.25)	8.0 (3.0–12.0)	7.0 (5.0–13.0)	0.64
Delay in diagnosis, years	5.0 (2.0–7.75)	4.3 (1.6–9.0)	5.0 (2.0–6.0)	0.97
Course of disease, years	15.5 (9.5–19.5)	17.5 (5.7–26.0)	15.0 (10.0–19.0)	0.78
Age at diagnosis of autoimmunity, years	4 (2.2–7)	4.5 (2.0–10.75)	4.0 (2.5–6.0)	0.94
Consanguinity, *n* (%)	25 (92.6)	10 (90.9)	15 (93.8)	1.0
Dead, *n* (%)	8 (29.6)	4 (36.4)	4 (25)	0.67

The median is shown (with 25th and 75th percentiles, IQR). M, male; F, female; IQR, interquartile range.

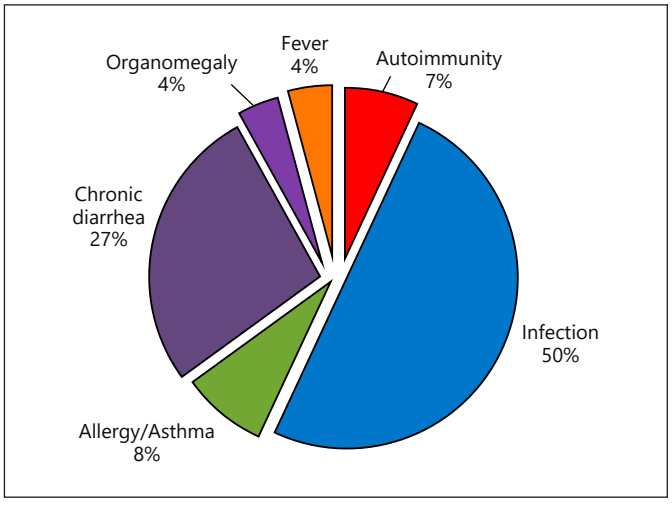

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Fig. 1. First presentation of monogenic primary immunodeficiency disorder associated with common variable immunodeficiency and autoimmunity.

Results

Baseline Demographic Data

A total of 27 patients (11 males [40.7%] and 16 females [59.3%]) with a mean (SD) age of 16.4 (±8.2) years were enrolled in this study (Table 1). The median (IQR) age at the onset of symptoms was 2.0 (0.6–3.0) years, and the mean (SD) age at the time of diagnosis was 8.3 (±6.0) years. The mean (SD) diagnostic delay was 5.7 (±5.2) years. Overall, 25 patients (92.6%) were born through consanguineous parents. At the time of the study, 8 (29.6%) individuals were deceased and the median follow-up for survived cases was 15.5 (±7.5) years. During the course of the disease, 11 patients (40.7%) were complicated with one type of autoimmunity and 16 patients (59.3%) developed poly-autoimmunity (more than one type of autoimmunity), of which 68.8% were female. The patients' characteristics are summarized in Table 1.

Genetic analysis as an inclusion criterion for this study was confirmed in all recruited 27 patients who were primarily diagnosed with CVID. The pathogenic variants were identified in *LRBA* (*n* = 17) and *DCLRE1C* (Artemis), *BLNK*, *BTK*, *DNMT3B*, *JAK3*, *MVK*, *RAG1*, *SH2DA1*, *XIAP*, and *IGHM* (μ heavy chain) each in 1 patient (Table 2).

Clinical Evaluation

As shown in Figure 1, the most prevalent first presentation of immunodeficiency in these patients was an infectious disease (*n* = 13, 50.0%) and chronic diarrhea (*n* = 7, 26.9%). Also, 2 patients (7.7%) showed autoimmune complications including ITP and AIHA, as the first clinical manifestation of the disease. In 13 patients (61.9%), the diagnosis of autoimmune disorders preceded the diagnosis of primary immunodeficiency, and in 7 (33.3%) patients, autoimmune complications were identified during the course of the disease (after diagnosis); while in 1 patient, the diagnosis was concurrent.

Gastrointestinal (*n* = 13, 48.1%), hematologic (*n* = 11, 40.7%), dermatologic (*n* = 6, 22.2%), and rheumatologic (*n* = 7, 25.9%) related autoimmunities were the most prevalent autoimmune manifestation in our CVID patients. Specific autoimmune entities included ITP (40.7%), AIHA (29.6%), RA/juvenile idiopathic arthritis (JIA) (25.9%), and inflammatory bowel disease (IBD, 22.2%)

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Table 2. General data on patients with monogenic primary immunodeficiency disorder associated with CVID and autoimmunity

Pts	Sex	Age, years	AoO, years	AoD-PID, years	AoD-Auto, years	D/A	Autoimmunity type	CD3, %	CD4, %	CD8, %	CD16-56, %	CD19, %	IgG, mg/dL	IgA, mg/dL	IgM, mg/dL	Gene mutation	Mutation type
P1	M	28.0	2.0	10.0	NA	A	AIE	74.0	18.0	55.0	11.0	6.0	360	0	44	*LRBA*	c.2836–2839del
P2	M	28.0	0.6	3.0	5.0	A	Vitiligo	NA	40.0	38.0	NA	NA	160	0	39	*BTK*	c.2010 + 5 G>A
P3	F	24.0	6.0	23.0	17.0	A	RA	55.0	36.0	18.0	18.0	11.0	675	113	71	*LRBA*	Large del 29–30
P4	M	6.0	1.0	1.0	2.0	D	Celiac	46.0	22.0	23.0	5.0	39.0	683	0	26	*JAK3*	c.2164G>A
P5	F	1.8	0.5	0.6	NA	D	ITP	69.0	31.0	19.0	2.0	19.0	617	16	50	*LRBA*	Hom c.1383_1384insAA AGTTAACGTTAGCAGAT AGAAGGAAATGATAAA
P6	M	13.0	NA	12.0	NA	A	Celiac	69.0	31.0	46.0	NA	8.0	203	62	100	*LRBA*	c.1540delG
P7	M	17.0	1.0	13.0	1.0	D	Vitiligo	85.0	36.0	36.0	NA	5.0	500	0	0	*SH2DA1*	ivs 1 + 1 G>A
P8	F	11.0	3.0	5.0	7.0	D	JRA	58.0	15.0	36.0	NA	10.0	480	9	28	*LRBA*	c.1014 + 1 C>T
P9	F	19.0	1.5	9.0	2.0	A	Alopecia areata	89.0	44.0	NA	3.0	1.1	212	6	2	*BLNK*	c.679C>T
P10	M	17.0	2.0	8.0	12.0	A	RA	64.0	8.0	54.0	8.0	1.0	68	0	15	*LRBA*	c.544C>T
P11	F	6.0	0.3	3.0	4.0	A	IBD	57.0	23.0	35.0	34.0	9.0	111	4	28	*LRBA*	Large deletion
P12	F	20.0	5.0	10.0	5.0	A	ITP/AIHA	77.0	32.0	26.0	NA	23.0	1,207	67	17	*LRBA*	c.4729 + 2dupT
P13	F	13.0	0.6	6.0	5.0	A	AIE/JRA	74.0	5.0	67.0	7.0	3.0	114	10	18	*LRBA*	c.5623delA
P14	F	22.0	3.0	11.0	8.0	A	ITP/AIHA/AIT/AIE	83.0	31.0	32.0	NA	7.0	565	5	69	*LRBA*	c.4729 + 2dupT
P15	M	13.0	0.5	4.0	2.5	A	ITP/AIHA	53.0	21.0	16.0	NA	2.0	96	16	35	*LRBA*	Large deletion exon 29-30
P16	M	18.0	2.0	5.0	5.0	A	ITP/Celiac	59.0	17.0	42.0	NA	0.0	340	0	401	*DCLRE1C*	c.41G>T
P17	F	20.0	8.0	13.0	19.0	D	Vitiligo/IBD	68.0	40.0	25.0	9.0	13.0	1,200	209	70	*LRBA*	Large deletion exon 29-30
P18	F	19.0	2.0	17.0	2.5	D	AIT/MG/celiac	42.0	31.0	19.0	NA	14.0	342	2	0	*LRBA*	Large deletion exon 1
P19	F	31.0	1.0	1.2	7.0	A	Psoriasis/JRA	94.1	68.3	19.7	3.0	0.0	355	19	9	*IGHM*	c.91C>T
P20	M	14.0	4.0	6.0	4.0	D	AIHA/ITP	87.0	55.0	20.0	7.0	6.0	320	19	40	*RAG1*	c.1073G>A
P21	F	8.0	0.0	0.9	NA	A	JRA/IBD	48.0	34.0	13.0	3.0	46.0	600	80	140	*MVK*	c.286G>A
P22	F	32.0	14.0	15.0	NA	A	ITP/AIHA/Alopecia	67.0	21.0	42.0	NA	21.0	15	10	1	*XIAP*	c.553G>A
P23	F	8.0	0.0	6.0	4.0	A	JRA/IBD	66.0	30.0	37.0	3.0	23.0	25	0	7	*DNMT3B*	c.2166T>A
P24	M	19.0	2.0	7.0	2.0	D	ITP/AIHA/AIE/IBD	88.0	32.0	55.0	NA	4.0	340	9	19	*LRBA*	c.175G>T
P25	F	2.0	NA	NA	NA	A	AIHA/ITP	63.0	NA	38.0	NA	NA	NA	NA	NA	*LRBA*	c.4638delC
P26	M	12.0	2.0	7.0	3.0	A	AIHA/ITP/EVANS	84.0	32.0	50.0	10.0	8.0	47	45	193	*LRBA*	c.743_744insAAGA
P27	F	22.0	1.0	21.0	2.0	A	AIH/IBD/ITP/MS	NA	NA	NA	NA	NA	500	7	145	*LRBA*	c.4814C>G

Pts, patients; M, male; F, female; Auto, autoimmunity; A, alive; D, dead; AoO, age at onset; Ao-PID, age at diagnosis of primary immunodeficiency disorder; AoD-Auto, age at diagnosis of autoimmunity; CVID, common variable immunodeficiency; ITP, idiopathic thrombocytopenic purpura; AIHA, autoimmune hemolytic anemia; RA, rheumatoid arthritis; JRA, juvenile rheumatoid arthritis; IBD, inflammatory bowel disease; AIE, autoimmune enteropathy; AIT, autoimmune thyroiditis; MG, myasthenia gravis; MS, multiple sclerosis; AIH, autoimmune hepatitis; NA, not available.

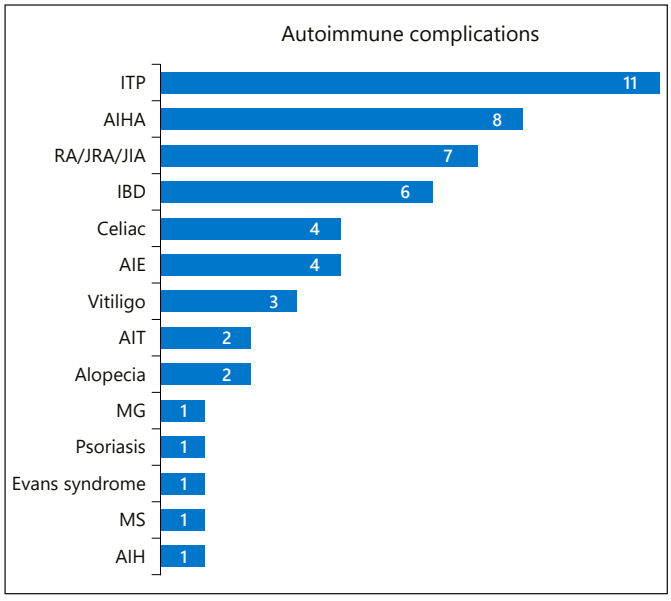

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Fig. 2. Autoimmune complications reported in CVID patients. CVID, common variable immunodeficiency; ITP, idiopathic thrombocytopenic purpura; AIHA, autoimmune hemolytic anemia; RA, rheumatoid arthritis; JRA, juvenile rheumatoid arthritis; JIA, juvenile idiopathic arthritis; IBD, inflammatory bowel disease; AIE, autoimmune enteropathy; AIT, autoimmune thyroiditis; MG, myasthenia gravis; MS, multiple sclerosis; AIH, autoimmune hepatitis.

(Fig. 2). In addition, both autoimmune neurologic and endocrine disorders were reported in 7.4% of our monogenic CVID-like patients.

Among 16 patients with poly-autoimmunity, 10 patients (62.5%) had 2 types of autoimmunity, 3 patients (18.8%) had 3 types of autoimmunity, and 3 patients had 4 types of autoimmunity. The most common overlapping syndrome was the combination of rheumatologic and gastrointestinal autoimmune disorders. In addition, the frequency of ITP (62.5 vs. 9.1%, $p = 0.008$) and AIHA (50.0 vs. 0.0%, $p = 0.008$) was higher than that of other autoimmune manifestations in patients with poly-autoimmunity than those with mono-autoimmunity.

Most of the patients with mono-autoimmunity primarily developed infectious complications including pneumonia ($n = 4$) and sinusitis ($n = 2$). While in patients with poly-autoimmunity, the most common first presentation was chronic diarrhea ($n = 6$). As illustrated in Table 3, the frequency of otitis media, sinusitis, pneumonia, skin infection, septicemia, bronchiectasis, failure to thrive, splenomegaly, hepatomegaly, clubbing, enteropathy, and allergy/asthma were reported more frequently in patients with poly-autoimmunity than mono-autoimmunity; however, the differences were not significant. Mortality was reported in 4 patients with poly-autoimmunity and in 4 patients with mono-autoimmunity.

Immunological Evaluation

The summary of immunological findings is represented in Table 4. Overall, lymphopenia was reported in 38.5% of patients. While most of the patients had a normal (66.7%) or elevated (29.2%) level of $CD3^+$ T lymphocyte, 34.8% of patients had low $CD19^+$ B lymphocytes. A low frequency of $CD4^+$ T cells and a high frequency of $CD8^+$ T cells were reported in 40.0 and 37.5% of patients, respectively. There was no statistical difference in immunoglobulin levels and B-cell and T-cell counts in CVID patients with or without poly-autoimmunity. The number of Treg cells was decreased in all poly-autoimmune patients, while 66.7% of patients with mono-autoimmunity had a low number of Treg cells.

Discussion

Autoimmune diseases can affect all subgroup classifications of primary immunodeficiency but are more frequently encountered in predominantly antibody defects, particularly CVID in which more than 20–30% of affected patients tend to develop autoimmune manifestations [3, 15]. Based on the ESID criteria, our patients were primarily diagnosed with CVID, but after genetic analysis via whole-exome sequencing, some patients with genetic defects in nonintrinsic B-cell pathways can be categorized as having combined immunodeficiency (CID) which presents the mild phenotype of the disease.

In our study, the first presentation of 7.7% of the selected group of CVID patients was autoimmunity, and in 61.9% of CVID patients, the diagnosis of autoimmune disorders preceded the diagnosis of immunodeficiency. Therefore, autoimmunity may be an alarming sign of the disease in pediatric CVID patients with no considerable history of severe and recurrent infections. Moreover, autoimmune disorders seem to be one of the first presentations of the monogenic forms of humoral immune disorders. It is crucial for physicians to be alerted about the main manifestations of CVID in order to reduce the diagnostic delay and establish timely Ig replacement therapy in these patients.

Autoimmune cytopenias are the most common organ-specific autoimmune diseases observed in primary im-

Table 3. Clinical manifestations of patients with poly-autoimmunity and mono-autoimmunity

Parameters	Total (n = 27)	Mono-autoimmunity (n = 11)	Poly-autoimmunity (n = 16)	p value
ITP	11 (40.7%)	1 (9.1%)	10 (62.5%)	0.008*
AIHA	8 (29.6%)	0 (0.0%)	8 (50%)	0.008*
AIE	4 (14.8%)	1 (9.1%)	3 (18.8%)	0.62
RA/JRA/JIA	7 (25.9%)	3 (27.3%)	4 (25%)	1.0
AIT	2 (7.4%)	0 (0.0%)	2 (12.5%)	0.49
Vitiligo	3 (11.1%)	2 (18.2%)	1 (6.3%)	0.54
Celiac	4 (14.8%)	2 (18.2%)	2 (12.5%)	1.0
Alopecia	2 (7.4%)	1 (9.1%)	1 (6.3%)	1.0
IBD	6 (22.2%)	1 (9.1%)	5 (31.3%)	0.35
MG	1 (3.7%)	0 (0.0%)	1 (6.3%)	1.0
Psoriasis	1 (3.7%)	0 (0.0%)	1 (6.3%)	1.0
Evans syndrome	1 (3.7%)	0 (0.0%)	1 (6.3%)	1.0
MS	1 (3.7%)	0 (0.0%)	1 (6.3%)	1.0
AIH	1 (3.7%)	0 (0.0%)	1 (6.3%)	1.0
Otitis media	17 (63%)	5 (45.5%)	12 (75%)	0.22
Sinusitis	17 (63%)	6 (54.5%)	11 (68.8%)	0.68
Pneumonia	21 (77.8%)	8 (72.7%)	13 (81.3%)	0.66
Skin infection	4 (14.8%)	0 (0.0%)	4 (25%)	0.12
Candidiasis	7 (25.9%)	3 (27.3%)	4 (25%)	1.0
Conjunctivitis	8 (29.6%)	3 (27.3%)	5 (31.3%)	1.0
Meningitis	7 (25.9%)	4 (36.4%)	3 (18.8%)	0.39
Septicemia	2 (7.4%)	0 (0.0%)	2 (12.5%)	0.49
Septic arthritis	6 (22.2%)	3 (27.3%)	3 (18.8%)	0.66
Bronchiectasis	12 (44.4%)	4 (36.4%)	8 (50%)	0.69
Neutropenia	1 (3.7%)	0 (0.0%)	1 (6.3%)	1.0
FTT	4 (14.8%)	1 (9.1%)	3 (18.8%)	0.62
Splenomegaly	15 (55.5%)	5 (45.5%)	10 (62.5%)	0.45
Hepatomegaly	13 (48.1%)	3 (27.3%)	10 (62.5%)	0.12
Lymphadenopathy	8 (29.6%)	3 (27.3%)	5 (31.3%)	1.0
Clubbing	6 (22.2%)	1 (9.1%)	5 (31.3%)	0.35
Malignancy	1 (3.7%)	1 (9.1%)	0 (0.0%)	0.40
Enteropathy	22 (81.5%)	8 (72.7%)	14 (87.5%)	0.37
Allergy/asthma	10 (37.4%)	3 (27.3%)	7 (43.8%)	0.44

ITP, idiopathic thrombocytopenic purpura; AIHA, autoimmune hemolytic anemia; RA, rheumatoid arthritis; JRA, juvenile rheumatoid arthritis; JIA, juvenile idiopathic arthritis; IBD, inflammatory bowel disease; AIE, autoimmune enteropathy; AIT, autoimmune thyroiditis; MG, myasthenia gravis; MS, multiple sclerosis; AIH, autoimmune hepatitis; FTT, failure to thrive. * p value is statistically significant <0.05.

munodeficiency, and reports suggest that these disorders are subsequently diagnosed in up to 50% of pediatric cases of refractory multilineage autoimmune cytopenia [16, 17]. ITP is the most common cytopenia followed by AIHA in patients with humoral immunodeficiency [18]. Some patients have both ITP and AIHA, a condition often referred to as Evans syndrome. In one large case series of patients with CVID, the incidence of ITP was reported to be 14.2%, AIHA, 7%, Evans syndrome, 4%, and autoimmune neutropenia, <1% [19]. This high prevalence of hematologic autoimmune manifestations in PID was also apparent within our cohort with 40.7% of participants developing hematologic autoimmune complications, including ITP (40.7%) and AIHA (29.6%); however, Evans syndrome as another hematologic autoimmune complication was mentioned for only 1 patient. This high level of association highlights the fact that patients referring to autoimmune cytopenia particularly those with a "difficult-to-treat" ITP or AIHA should be evaluated for humoral immunity.

It was reported that about 25% of patients with autoimmune diseases have a tendency to develop addi-

tional autoimmune diseases [20]. In "multiple autoimmune syndromes," patients often have at least 1 dermatological condition commonly alopecia areata or vitiligo [21]. In our study among monogenic patients, 59.3% had poly-autoimmunity. In contrast to conventional "multiple autoimmune syndromes" which usually develops dermatological condition [21], ITP and AIHA were the most 2 concomitant autoimmune disorders in our monogenic patients. The high frequency of autoimmune cytopenias in gene-specific defects was also reported in previous studies, especially in patients with *LRBA* deficiency [22, 23]. Our result showed that 58.8% of patients with *LRBA* deficiency have poly-autoimmunity. It is in line with our previous study that showed 62.5% of *LRBA*-deficient patients had poly-autoimmunity [22]. In these patients, autoimmune cytopenias were the most frequent complication. Finally, in young patients with poly-autoimmunity and enteropathy with a history of chronic infection or hypogammaglobulinemia, the probability of *LRBA* deficiency must be considered by clinical immunologists.

Conclusion

The identification of an increasing number of genetic defects that are associated with autoimmunity and primary humoral immunodeficiency is providing insight into molecular pathways and mechanisms that promote immune dysregulation. Early recognition and treatment of these symptoms are critical for optimizing the quality of life and decreasing complications associated with CVID. This requires that patients and their care providers be aware of signs and symptoms that may suggest an autoimmune disease and that appropriate diagnostic testing and treatment be initiated in a timely fashion. ITP, AIHA, and autoimmune enteropathy are of the most prevalent features of monogenic defects resembling CVID, especially in patients with a positive family history of immunodeficiency, parental consanguinity, and/or recurrent infections. Two clinical clues that may suggest poly-autoimmunity in a patient with PID are either the development of autoimmune disorder at an early age or a low number of Tregs. Autoimmunity carries high morbidity and mortality in patients with CVID; therefore, awareness of these monogenic forms of poly-autoimmunity together with the implementation of precision medicine will allow prompt diagnosis and optimal treatment.

Table 4. Immunological profile of the patients with poly-autoimmunity and mono-autoimmunity

Parameters	Total	Mono-autoimmunity	Poly-autoimmunity	*p* value
WBC, $\times 10^3$ cells/μL ($n = 27$)	7,390.0 (5,300.0–12,100.0)	8,700.0 (5,500.0–14,400.0)	6,950.0 (5,217.5–10,057.5)	0.50
Hb	12.0 (9.0–13.1)	12.1 (9.0–13.2)	12.0 (8.7–13.7)	0.73
Absolute lymphocyte counts, $\times 10^3$ cells/μL ($n = 27$)	1,960.0 (1,632.0–3,360.0)	2,016.0 (1,632.0–2,800.0)	1,896.5 (1,328.0–4,255.5)	0.73
Lymphocytes, %	34.0 (23.0–49.0)	33.0 (21.0–48.0)	34.5 (24.0–62.0)	0.36
Absolute neutrophil counts, $\times 10^3$ cells/μL ($n = 27$)	4,161.0 (2,458.7–6,841.0)	4,877.0 (2,940.0–7,986.0)	3,712.0 (1,710.0–6,825.0)	0.33
Neutrophils, %	53.0 (41.7–66.0)	59.0 (45.0–66.0)	49.0 (32.0–65.0)	0.19
$CD3^+$ T cells, $\times 10^3$ cells/μL ($n = 25$)	68.0 (57.5–83.5)	66.5 (56.5–76.7)	68.0 (59.0–84.0)	0.59
$CD4^+$ T cells, $\times 10^3$ cells/μL ($n = 25$)	31.0 (21.0–36.0)	31.0 (18.0–36.0)	31.5 (21.0–35.5)	0.68
$CD8^+$ T cells, $\times 10^3$ cells/μL ($n = 25$)	36.0 (19.8–44.0)	36.0 (22.0–48.0)	32.0 (19.7–42.0)	0.71
$CD16^+/56^+$ NK cells, $\times 10^3$ cells/μL ($n = 14$)	7.0 (3.0–10.25)	8.0 (3.0–18.0)	7.0 (3.0–9.0)	0.43
$CD19^+$ B cells, cells/μL ($n = 24$)	8.0 (3.25–17.75)	8.5 (4.0–13.0)	7.5 (2.7–21.5)	0.95
IgG, mg/dL ($n = 26$)	341.0 (113.25–573.75)	360.0 (160.0–617.0)	340.0 (96.0–565.0)	0.64
IgA, mg/dL ($n = 26$)	9.0 (0.0–25.5)	4.0 (0.0–16.0)	10.0 (5.0–45.0)	0.11
IgM, mg/dL ($n = 26$)	31.5 (13.5–70.75)	28.0 (15.0–50.0)	35.0 (9.0–140.0)	0.71
IgE, IU/mL ($n = 16$)	0.0 (0.0–3.0)	0.5 (0.0–4.2)	0.0 (0.0–4.0)	0.81

The median is shown (with 25th and 75th percentiles, IQR). Ig, immunoglobulin; WBC, white blood cells; NK cells, natural killer cells; IQR, interquartile range.

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Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of Tehran University of Medical Sciences. Informed written consent was obtained from all individuals included in the present study.

Author Contributions

M.H.A. wrote the manuscript. G.A. performed the statistical analysis. R.Y. performed the first revision of the manuscript. H.A. and N.R. performed the final revision of the manuscript. A.A. was responsible for supervision and approved the final version of the manuscript. The rest of the authors were responsible for data collection.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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