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Autoimmunity Complications in Common Variable Immunodeficiency (CVID) Patients; an update from the Iranian registry

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Abstract

Background/objectives: CVID is known as the most prevalent symptomatic primary immunodeficiency (PID) characterized by heterozygous manifestations including several infectious and non-infectious complications. Accordingly, although the hallmark of this disease is the development of recurrent sinopulmonary infections, different types of autoimmunity are frequently reported in CVID subjects. So in this study, we aimed to provide an update report on various autoimmunity manifestations in a group of CVID patients in Iran.

Methods: Demographic, clinical, and immunologic data of Iranian CVID cases who were followed up at children's medical center were collected. Based on the presence of autoimmunity, the patients were then divided into two groups of autoimmunity and non-autoimmunity for further analyses.

Results: Among 301 CVID cases enrolled in this study, 81 (26.9%) had autoimmunity that was mostly manifested as autoimmune cytopenia; 21 (24%) out of these 81 individuals had immune thrombocytopenic purpura (ITP) and 14 (17.3%) patients showed autoimmune hemolytic anemia (AIHA). Moreover, Rheumatologic autoimmune disorders such as Juvenile Idiopathic Arthritis (JIA) and Juvenile Rheumatoid Arthritis (JRA) were observed in 7 (8.6%) and 5 (6.2%) individuals, respectively. Also, inflammatory bowel disease in 6 subjects (7.4%) and vitiligo in 7 patients (8.6%) were the most observed gastrointestinal and dermatologic autoimmune disorders in this study. Accordingly, some of these conditions were concomitant in a single individual. Additionally, several significant correlations were observed between autoimmunity and other complications including sinusitis (P=0.04), Bronchiectasis (P=0.002), Chronic diarrhea (P=0.000), and thrombocytopenia (P=0.000).

Conclusion: Autoimmunity and its association with other clinical manifestations should be paid more attention among CVID patients.

Keywords: autoimmune complications, common variable immunodeficiency, primary immunodeficiency, immune thrombocytopenic purpura

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Introduction

Common Variable Immunodeficiency (CVID) is known as the most prevalent form of primary immunodeficiencies (PID) with an incidence of 1:50,000 to 1: 25,000 individuals. In addition, it is characterized by a significant defect in antibody response against polysaccharide pathogens and the reduced number of B lymphocytes, and especially memory B cells. Also, CVID is a heterogonous disorder, which can affect the patients presenting broad range of clinical conditions including infectious and non-infectious symptoms. The patients mostly manifest the disease by developing sinopulmonary infections such as sinusitis, otitis, and pneumonia (1). Although upper and lower respiratory tract infections are known as the most common types of complications in these patients, autoimmune conditions are also reported to have the incidence rate of 21-42 % in all CVID cases (2). The pathogenesis of autoimmunity in CVID is poorly understood and appears to be paradoxical; because the patients affected by this disease are unable to produce- or little produce- antibodies against pneumococcal antigens, tetanus, or diphtheria vaccination. while they produce autoantibodies against internal tissues at the same time (3). Moreover, the intravenous immunoglobulin (IVIG) treatment therapy, which significantly resolves infections and sinopulmonary conditions, alleviates no autoimmune/inflammatory complications. Moreover, it would not decrease the mortality and morbidity rates caused by autoimmunity (4). Thus, management of autoimmunity in CVID patients requires more considerations since concomitance of immunodeficiency and dysregulation of the immune system impair the diagnosis and treatment processes (2). Notably, the onset of autoimmunity varies, as well as the progression and severity of condition in each CVID patient (5). Autoimmunity might be the first presentation of CVID disease with no prior history of severe infections (6-8). In this regard, different types of autoimmunity could be categorized into five groups as follows: hematologic, gastrointestinal, pulmonary, rheumatologic, and dermatologic disorders (4). Also, the most prevalent forms of autoimmunity in CVID cases are immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA), both of which are hematologic disorders. Accordingly, these complications usually occur individually and sometime concurrently as the case of Evan's syndrome (9). Gastrointestinal inflammatory conditions are the other common autoimmune disorders in CVID patients occurring in the stomach, small and large bowel, and the liver. Moreover, atrophic gastritis, chronic enteropathy, and inflammatory bowel disease

(IBD) are the most significant in the above-mentioned category (10-12). Rheumatologic diseases that involve joints of knees, ankles, and hands are commonly seen as adult's rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), and juvenile idiopathic arthritis (JIA) among CVID cases. Notably, less frequent types of rheumatological autoimmunity are lupus erythematosus, Bechet's disease, and Sjogren's syndrome (13-15). Additionally, autoimmune Skin involvement in CVID include psoriasis, vitiligo, alopecia, and lichen planus (7, 16, 17).

Given the importance of autoimmune complications in CVID and the consequences of the delayed diagnosis and treatment for this disease; in the present study, we aimed to review the obtained demographic and lab data and autoimmunity status in a group of Iranian CVID patients.

Material and Methods

Study population

A total of 301 CVID patients referred to Children's medical center (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran) were enrolled in this study. The diagnosis of CVID in these patients was performed based on the newest European Society of Immune Deficiencies (ESID) criteria and was then followed by the significant decrease of IgG and IgA with or without low IgM, poor antibody response to vaccines or low switched memory B cells, the increased susceptibility to infection, autoimmunity, granulomatous disease, and unexplained polyclonal lymphoproliferation (https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria).

Data Collection

With ethical considerations, comprehensive data of the patients were collected using a questionnaire as follow: (a) demographic data (including gender, age, age of onset, age of diagnosis, delay in diagnosis, course of disease and follow-up, and consanguinity) (b) Clinical manifestations (infections, gastrointestinal complications, enteropathy, allergy, lymphoproliferative disorders, autoimmunity, and malignancy), and (c) laboratory findings (complete blood count (CBC), Immunoglobulin levels, and evaluation of lymphocyte subsets). Afterward, based on the presence of autoimmunity complications, the patients were divided into two autoimmune and non-autoimmune patients' groups.

Statistical analysis

Analysis of the obtained data was performed using SPSS 22 software (SPSS Inc., Chicago, IL, USA). Also, Shapirowilk and Kolmogrove Smirnov tests were used to check the normality of data. Frequencies are reported as median (interquartile range, IQR). Afterward, to compare numerical variables of parametric and non-parametric distribution, independent sample T-test and Mann-Whitney tests were used, respectively. Moreover, for 2×2 comparison of variables, chi-square and Fisher's exact tests were used.

Results

Demographic and laboratory data

In this study, a total of 301 patients with CVID (173 men and 128 women) with median age of 24 years old (ranged from 15 to 31 years old) were enrolled. Accordingly, 81 (26.9%) patients had autoimmunity and the remaining 221 patients (73.2%) had no autoimmune disorders. Demographic data of CVID patients with or without autoimmunity as well as their analytical comparisons are depicted in **Table 1**. As shown in this table, there was a significant correlation in the mortality rate between autoimmune (28%) and non-autoimmune (15.5%) patients (P=.01). Similarly, a significant correlation was also observed in consanguinity (P=.01) among the autoimmune (65%) and non-autoimmune patients (50%). Moreover, analysis of complete blood count (CBC) revealed a significant decrease in White Blood Cell (WBC) count in autoimmune

subjects (6850 cell/µl) compared with non-autoimmune (8515cell/µl) individuals (P=.002). Additionally, as expected in autoimmune cases, a significant decrease was observed in their platelet counts (189500 cell/µl) compared with non-autoimmune cases (241000 cell/µl) (P=.005). Also, the IgM levels in the patients with autoimmunity (34mg/dl) significantly increased compared to the patients without any autoimmunity (26mg/dl) (P=.05).

Table 1. Demographics and laboratory data of total CVID patients, those with and without autoimmunity, as well as their comparison

Parameters		Total (N=301)	With autoimmunity (N=81)	Without autoimmunity (N=220)	P-value
Sex	Male; N (%)	173 (57.5%)	40 (49.4%)	133 (60.5%)	.09
	Female; N (%)	128 (42.5%)	41 (50.6%)	87 (39.5%)	
Status	Dead; N (%)	57 (18.9%)	23 (28%)	34 (15.5%)	.01*
	Alive; N (%)	204 (67.8%)	50 (61%)	154 (70%)	
Consanguinity; N (%)		165 (54.8%)	53 (65%)	112 (50%)	.01*
Median age; years old (IQR)		24 (15-31)	22 (16.25-31)	24 (14-32)	.839
Median age; month (IQR)		288 (180-375)	264 (195-372)	288 (168-387)	.843
Median AOO; month (IQR)		24 (6-86)	24 (7-90)	19 (6-84)	.39
Median AOD; month (IQR)		108 (36-230)	108 (45-243)	108 (25-229)	.57
Median DOD; month (IQR)		48 (12-105)	46 (12-93)	48 (12-108)	.94
Course of disease; month (IQR)		189 (60-288)	206 (97-256)	182 (43-298)	.4
Median Follow up; month (IQR)		131 (12-198)	147 (678-194)	125 (11-204)	.29
Median Follow up; year (IQR)		13 (6-17)	13 (6.5-16.5)	12 (5.6-23.25)	.79
WBC, cell/µl		7855 (5465-10975)	6850 (4480-8925)	8515 (5900-11300)	.002*
Lymphocyte, %		35 (24.6-50)	33 (24-51)	36 (25-50)	.48
Neutrophil		55 (41-67)	56 (44.7-67)	54 (40-67)	.41
Hb		12 (11-13)	12 (11-13)	12 (11-13)	.32
Platelet, cell/µl		231000 (117000-321500)	189500 (443-314500)	241000 (151000-331000)	.005*
CD3, %		74 (63-83)	76.9 (66-85)	74 (63-81)	.24
CD4, %		32 (23-42)	32 (22-40)	32 (24-42)	.45
CD8, %		35 (25-50)	37 (25-51)	34.5 (25-49)	.28
CD56, %		6 (3-10)	8 (2-11)	6 (3.5-9.7)	.66
CD16, %		7 (5-11.5)	8 (4.5-13.5)	7 (5-17)	.35
CD19, %		9 (4-17)	6 (3-14.5)	10 (4.25-18)	.04*
CD20, %		11 (4-20)	10.5 (3-15.25)	12 (5-20)	.23
IgG, mg/dl		222 (76-470)	252.5 (72-497)	216.5 (74.5-443.5)	.45
IgM, mg/dl		28 (13-59)	34 (18.2563)	26 (11.5-54)	.05*
IgA, mg/dl		19 (6.75-46.25)	16 (8-44)	19 (6-47)	.83
IgE, IU/ml		1 (0-5)	1 (0-7)	1.36 (0.3-5)	.57

IRQ: Inter Quartile Range (25th and 75th)
AOO: Age of Onset; AOD: Age of Diagnosis; DOD: Delay of Diagnosis: WBC: White Blood Cell; Hb: Hemoglobulin

Table 2. clinical manifestations of CVID patients, those with and without autoimmunity, as well as their comparison

Parameter	Total (N=301)	With autoimmunity (N=81)	Without autoimmunity (N=220)	P-value
Recurrent Infection	176 (58.5%)	52 (64%)	124 (56%)	0.2
Otitis	145 (48.2%)	45 (55.5%)	100 (45%)	0.12
Pneumonia	207 (68.8%)	59 (72%)	148 (67%)	0.35
Sinusitis	149 (49.5%)	48 (59%)	101 (45%)	0.04*
Respiratory tract infection	250 (83.1%)	71 (87.5%)	10 (4.5%)	0.19
Bronchiectasis	86 (28.6%)	34 (41%)	52 (23.6%)	0.002*
Clubbing	71 (23.6%)	29 (35%)	42 (19 %)	0.002*
Lymphoproliferative	83 (27.6%)	38 (45%)	45 (20.45%)	0.000*
Oral ulcer	45 (15%)	15 (18.5%)	30 (136%)	0.29
Chronic diarrhea	118 (39.2%)	48 (59.2%)	70 (31.81)	0.000*
Allergy	63 (20.9%)	23 (28.3%)	40 (18.18%)	0.05*
Malignancy	14 (4.7%)	5 (6.2%)	9 (4.1%)	.02
Failure to thrive	72 (23.9%)	26 (32%)	46 (20.9)	0.04*
Conjunctivitis	40 (13.3%)	20 (24.6%)	20 (9%)	0.000*
Tooth decay	10 (3.3%)	5 (6.1%)	5 (2.27%)	0.09
Candidiasis	51 (16.9%)	21 (26%)	30 (13.6%)	0.12
Urinary tract infections	47 (15.6%)	22 (27.1 %)	25 (11.3%)	0.03*
Meningitis	8 (2.7%)	3 (3.7%)	5 (2.27%)	0.48
Hematologic	69 (23%)	39 (48.1%)	30 (13.63%)	0.000*
Anemia	49 (16.3%)	27 (33.33%)	22 (10%)	0.000*
Neutropenia	18 (6%)	10 (12.34%)	8 (3.6%)	0.02*
Thrombocytopenia	26 (8.6%)	19 (23.4%)	7 (3.1%)	0.000*
Leukopenia	12 (4%)	8 (9.8%)	4 (1.8%)	0.007*
Gastrointestinal complications	215 (71.4%)	66 (81.4%)	149 (67.7 %)	0.04*
Musculoskeletal	23 (36.9%)	12 (14.8%)	11 (5%)	0.02*
Pan cytopenia	18 (6%)	11 (13.5%)	7 (3.1%)	0.004*
Dermatologic	112 (37.2%)	44 (54.3%)	68 (31%)	0.06

Clinical Manifestations

Notably, respiratory tract infections followed by lower respiratory tract infection (Pneumonia) and gastrointestinal complications were the most frequent clinical manifestations in all CVID patients (83.1%, 71.4%, and 68.8%, respectively) as shown in **Table 2**. More specifically, upper and lower tract respiratory infections as well as the chronic diarrhea were the most observed first presentations of the disease in our study group (27.94%, 26.74%, and 20.22%, respectively). Accordingly, data on the first presentations are completely shown in **Figure1**. Also, detailed data on clinical manifestations in CVID patients, and the patients with or without autoimmunity as well as their analytical comparisons are represented in **Table 2**. Moreover, autoimmunity was observed in 81(26.9 %) patients. Comparison of these manifestations between the autoimmune and non-autoimmune individuals showed a significant correlation under several clinical conditions. Out of infections, sinusitis, bronchiectasis, and urinary

tract infection have significantly increased in the patients with autoimmunity (P=.04, .002 and .03, respectively). In addition, gastrointestinal complications (P=.04), chronic diarrhea (P=.000), and lymphoproliferation (P=.000) were more frequent in autoimmune individuals compared to the others. Also, hemolytic complications including anemia (P=.000), neutropenia (P=.02), leukopenia (P=.007), and pancytopenia (P=.004) have significantly increased in the patients with autoimmune disorders. Allergy (P=.05), failure to thrive (P=.04), conjunctivitis (p=.000), and malignancy (P=.02) were other manifestations that significantly increased in CVID cases with autoimmunity.

Different types of autoimmunity disorders

Many forms of autoimmunity were observed in our cases; however, the common ones were Idiopathic thrombocytopenia purpura (ITP) in 24% of the patients, and Autoimmune hemolytic anemia (AIHA) in 17.3% of them that are considered as hematolytic disorders. Besides, other autoimmune complications with a relatively high rate were Juvenile Idiopathic Arthritis (JIA) with a prevalence rate of 8.6%, vitiligo with 8.6%, and Inflammatory bowel disease (IBD) with a rate of 7.4%. Of note, these disorders occurred individually or occasionally in a concomitant manner. **Table 3** depicts the frequency of different types of autoimmunity in this study.

Table3. Different types of autoimmunity among CVID patients

Parameter	N= 81
Immune Thrombocytopenic Purpura (ITP)	21 (24%)
Autoimmune Hemolytic Anemia (AIH)	14 (17.3%)
Rheumatoid Arthritis (RA)	3 (3.7%)
Juvenile Idiopathic Arthritis (JIA)	7 (8.6%)
Juvenile Rheumatoid Arthritis (JRA)	5 (6.2%)
Inflammatory Bowel disease (IBD)	6 (7.4 %)
Vitiligo	7 (8.6%)
Psoriasis	3 (3.7%)
Systemic Lupus Erythematous (SLE)	2 (2.5%)
Celiac	6 (7.4%)
Lichen plans	2 (2.5 %)
Alopecia	4 (4.9%)
Guillain-Barré syndrome (GBS)	3 (3.7%)
Hashimoto's disease	2 (2.5%)
Crohn's disease	2 (2.5%)
Kawasaki syndrome	1 (1.23)
Insulin-Dependent Diabetes Mellitus	1 (1.23)

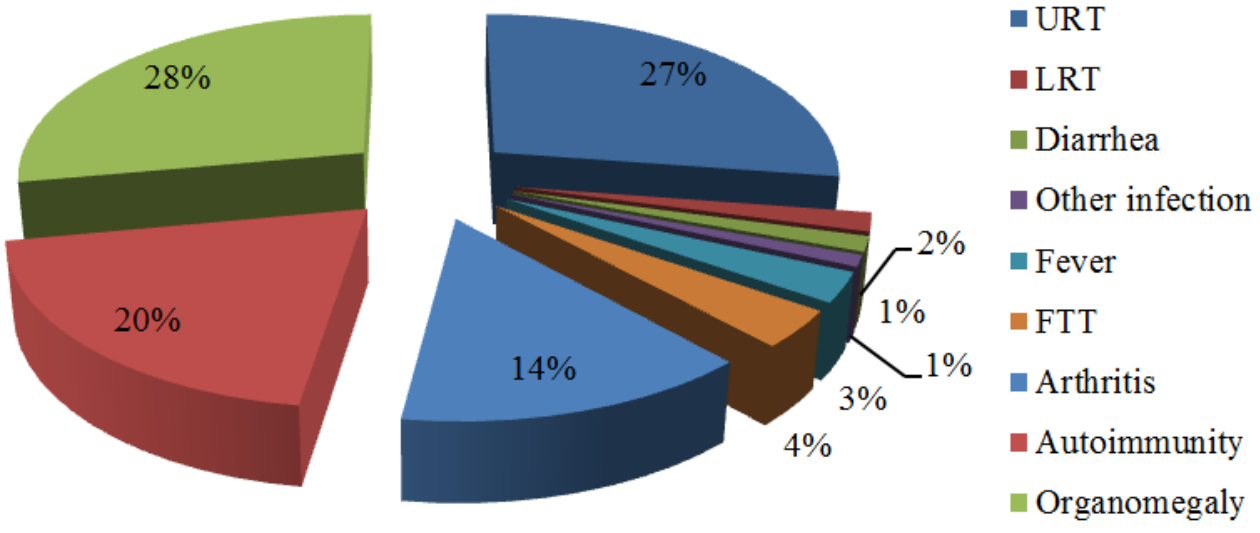

Figure1. First presentations in 301 CVID patients. UTR: Upper Respiratory Tract infection, LRT: Lower Respiratory Tract infection, and FTT: Failure to Thrive

Discussion

In the present study, we evaluated the frequency of autoimmune disorders as well as their correlation with demographic, lab data, and other clinical manifestations in a cohort of 301 CVID patients who were followed-up for a 13-year period.

26.9% of our patients had one or more autoimmune manifestations, 65% of whom were from the related parents. In line with our study, Brandt et al. (2009) suggested that certain genetic disposition in combination with repeated antigen exposure and overall immune dysfunction can increase the risk of autoimmunity in CVID cases (18). Another study conducted on a group of Iranian CVID cases also reported that the patients with consanguine parents were more affected by autoimmune complications (19). Thus, the association between autoimmunity and CVID might be due to a pathogenic genetic reason, rather than post-infectious immunopathogenic influence or epigenetic factors.

Our results show that the survival rate was significantly lower in CVID patients with autoimmunity compared to non-autoimmune patients. Moreover, the common treatment approach for CVID, which enhances survival in most patients, is the replacement of Ig at frequent intervals (20). Although Ig therapy reduces a large number of infectious complications (21) in CVID patients, it fails in protecting them against non-infectious complications including autoimmunity and gastrointestinal inflammatory bowel diseases (6, 7, 22). A study conducted on mortality and morbidity among 473 American subjects who were followed up over 4 decades revealed that the risk of death was 11 times higher in the patients with non-infectious complications. However, the mortality was associated with gastrointestinal diseases, hepatitis, and lymphoma, not with the history of autoimmunity alone (23). According to our results and previous studies, when evaluating mortality among CVID patients, it was revealed that, those with at least one non-infectious complications including autoimmune, pulmonary, gastrointestinal, lymphoproliferation, and malignant conditions are at higher risk of mortality (7, 23, 24).

We found that, IgM levels have significantly increased in autoimmune positive cases. Chapel et al. (2008) reported the association among the increased levels of IgM and the development of lymphoid malignancy and polyclonal lymphocytic infiltration (7). On the other hand, we observed a significant correlation between autoimmunity and the decrease in $CD19^{+}$. By considering that in most CVID cases the switched memory B cells have decreased (25), it could be suggested that the defect in class switch recombination leads to the increased levels of IgM and consequently to autoimmunity.

A strong correlation was also observed between autoimmunity and decrease in WBC and platelet count in this study. Additionally, different forms of pan cytopenic complications including thrombocytopenia, leukopenia, and neutropenia have significantly increased in the autoimmune positive patients. Interestingly, in consistent with these findings, autoimmune thrombocytopenia and hemolytic autoimmune anemia were the most observed types of autoimmunity among our cases. Several studies have reported that autoimmune cytopenia most frequently occur in CVID cases, either separately or concurrently (3, 6, 26, 27).

Gastrointestinal autoimmune complication was also frequent in our cases. Consistently, a strong correlation was observed among autoimmunity, chronic diarrhea, and lymphoproliferation. Moreover, Enteropathies and inflammatory Bowel disease (IBD)-like diseases have been reported in 6% to 10% of the patients with CVID (6). The largest lymphoid organ in the body that is directly connected with microbial pathogens is gut-associated lymphoid tissue. In addition, it is suggested that microbial biodiversity of CVID patient's gut has reduced. Also, impaired immunity across the gut barrier increase microbiome translocation leading to persistent immune activation and consequently systemic inflammation and immune dysregulation (28-30).

JIA was another high rate autoimmune disorder in our cases. Furthermore, several studies have reported the association between CVID and rheumatologic diseases (7, 13, 23). In a study conducted on the 870 CVID patients from the USIDNET registry (31) , rheumatologic disease was accounted for 40% of the autoimmune disorders of this cohort, of them adult and juvenile inflammatory arthritis were the most reported autoimmunity manifestation, with approximately 3% prevalence rate among the patients (13). Similarly, in a study by Abolhassani et al., it was that reported that, juvenile rheumatoid arthritis and autoimmune cytopenia were the most observed autoimmune disorders in a group of Iranian CVID patients, which were significantly correlated with polyclonal lymphocytic infiltrative disorders (14).

Conclusion

Autoimmune complications are considered as sever manifestations that are rarely observed in CVID patients. Upon persistent and progression, these disorders incur some difficulties in the management and regular treatment of CVID. Therefore, performing studies on the effect of autoimmunity and their association with other manifestations could help in better understanding of these conditions.

Conflicts of interest

The author declare that they have no conflicts of interest.

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