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Retrospective Analysis of Autoimmune Diseases and Immunologic Characteristics of the Adult Primary Immune Deficiency Cohort: 17 Years Experience of the Tertiary Referral Immunology Center in Turkey

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ABSTRACT

Objective: Primary immunodeficiencies (PIDs) consist of genetically heterogeneous disorders. The spectrum can include infectious diseases, malignancy, allergy, and autoimmunity. We aimed to analyze the frequency and variety of autoimmune diseases (ADs) in PIDs and describe their clinical and laboratory features.

Materials and Methods: Ninety-two patients with PID followed by Ege University Medical Faculty between 2000 and 2017 were enrolled in this retrospective, cross-sectional study. All patients' medical records were reviewed using the demographic information, type of PIDs and ADs, ADs-related autoantibodies, and basic and immunologic laboratory findings. ADs were diagnosed using clinical and complementary paraclinical findings by an immunologist and/or a subspecialist related to the affected organ or system.

Results: We evaluated 50 male and 42 female PID patients with a mean age of 40.92 (18-86). Twenty-nine (32 %) patients (15 females/14 males) with a mean age of 43.8 (19-78) had ADs. In our study group, the most commonly detected type of PID with AD is common variable immune deficiency (CVID) (n=17); followed by combined immune deficiency (CID) (n=3), CTLA4 deficiency (n=2), selective IgA deficiency (sIgAD) (n=2), specific IgG subgroup deficiency (n=1), autoimmune polyglandular syndrome (APS) with hypogammaglobulinemia (n=1), dyskeratosis congenita (DC) (n=1), Osler-Rendu-Weber (ORW) syndrome with CVID-like PID (n=1), and cartilage-hair hypoplasia (CHH) (n=1). According to systematic assessments, ADs resulted in endocrinologic 14%, dermatologic 10.8%, rheumatologic 9.7%, gastroenterological 9.7%, hematological 8.6%, and neurologic disorders 1%. The frequency of ADs was higher in CVID cases than other types of PIDs ($p < 0.05$). Basic and immunologic laboratory findings of the PIDs with and without ADs were analyzed and compared; however, no statical significant difference was obtained between the groups.

Conclusion: We have analyzed the frequency and variety of ADs in a adult PID cohort in Turkey. Patients presenting with multiple ADs should be screened for having an underlying PID.

Keywords: Primary immune deficiency, autoimmunity, autoantibody, immunologic parameters, frequency

INTRODUCTION

Clinical spectrum of primary immunodeficiencies (PIDs) is diverse and can include manifestations such as infectious diseases, malignancy, allergy, and autoimmunity (1). The first description of PID appeared in 1952 when Ogden Bruton discovered X-linked agammaglobulinemia (XLA). Since then, more than 350 unique PIDs have been identified (2). Several studies have shown that autoimmune diseases (ADs) are the second most common clinical consequence of PIDs (3-6). Common variable immune deficiency (CVID) and selective IgA deficiency (sIgAD) are frequently associated with ADs (6). Moreover, several PIDs are associated with defects in the frequency and

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function of T regulatory (Treg) cells and the production of autoantibodies.

ADs have been reported in 20-25% of patients with CVID (7,8). Manifestations of proven or suspected autoimmune mechanisms associated with CVID are hematologic [autoimmune cytopenias, autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenic purpura (ITP), autoimmune neutropenia (AIN)], gastroenterological [pernicious anemia (PA), celiac-like enteropathy (CLE), primary biliary cirrhosis (PBC), inflammatory bowel disease (IBH)], rheumatologic [Sjogren syndrome (SS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), chronic juvenile arthritis, vasculitis], endocrinologic [autoimmune thyroid disease (AITD), insulin-dependent diabetes mellitus (IDDM)], dermatologic [vitiligo, alopecia, chronic spontaneous urticarial (CSU)], and neurologic (Guillain-Barré syndrome) (9). Biologic analyses reveal hypogammaglobulinemia, a variable T cell phenotype, and a normal B cell count in most cases (10).

Many pathogenetic mechanisms of autoimmune diseases have previously been identified. In ADs, the central and peripheral tolerance of the adaptive immunity is defective. To clarify, the induction of T cell tolerance, the activation of programmed cell death, the clearance of the autoreactive T cells by apoptosis, the function of regulatory T cells, and the clearance of the self-reactive B cells are impaired. All of the defective ways of the immune system result in the production of autoreactive cell clones. Other pathogenic mechanisms make PIDs more susceptible to ADs. These are composed of the mutated genes of the immune cell subsets, uncurable chronic infections and chronic inflammation, the accumulation of apoptotic cells, and the uncleansable immune complexes (11-16).

In our study, we aimed to analyze the frequency and variety of autoimmunities in PIDs and describe the PIDs' clinical and laboratory features.

MATERIALS and METHODS

Patients

This retrospective, cross-sectional study was performed using the data of 92 patients with PIDs who were diagnosed and followed by Ege University Medical Faculty, Department of Internal Medicine, Division of Allergy and Clinical Immunology, during 2000-2017 years. Clinical immunologists confirmed all PIDs' diagnosis by evaluating the clinical manifestations' compatibility with immunologic and genetic evaluations for all patients. The diagnosis of PIDs was based on the European Society for Immunodeficiency diagnostic criteria (17). The study was reviewed and approved by the Ege University ethics committee (number: 70198063-050.06.04). Written informed consent was obtained from all of the patients.

Methods

We designed a comprehensive questionnaire that included; age and gender of patients, type of PIDs and ADs, ADs-related autoantibodies, and PIDs' basic and immunologic laboratory features.

Laboratory evaluations were performed as indicated for each case, including complete blood count, peripheral blood smear, immunoglobulins and IgG subclasses serum levels, and isohemagglutinin tests. Specific antibody response to polysaccharide (pneumococcal polyvalent vaccine) and protein (tetanus and diphtheria vaccines) antigens were measured by the enzyme-linked immunosorbent assay method (18). Flow cytometry evaluation of lymphocyte subtypes, lymphocyte proliferation test (using tuberculin purified protein derivative, mitogens phytohemagglutinin, lipopolysaccharide E. coli), granulocyte function tests (chemotaxis, opsonization, oxidative burst, nitro blue tetrazolium dye test, phagocytosis, and killing), complement component and hemolytic titration of complement components (C3, C4, CH50), and DNA sequencing were assessed to confirm the diagnosis.

Genetic Analysis

Next-generation sequencing was used for diagnostic assays. The results were analyzed by a community designed ready to use "AmpliSeq Primary Immune Deficiency Research Panel v2 (©Illumina, Inc.)" including 264 genes and 5241 amplicons.

Immunological Analyses

The quantitative evaluation of serum immunoglobulins was performed by particle-enhanced immunonephelometry using the Behring Nephelometer II Analyzer (BNII) (©Dade Behring Marburg Gmbh). Complete blood counts were performed with Sheath reagent using the Abbott Cell Dyn 3700 series (USA).

A blood sample was used to determine complete B and T cell phenotypes at the Immunology Laboratory of the Ege University, Division of Allergy and Clinical Immunology. Peripheral blood lymphocyte subsets were

measured using the BD FACSCanto II flow cytometer with an eight-color configuration (San Jose, CA, USA) with fluorescent-labeled antibodies. For immunofluorescence staining, fresh EDTA whole blood samples were stained at room temperature using predetermined saturating concentrations of antibodies (Abs) for 15 minutes, and blood erythrocytes were lysed after staining using FACS Lysing solution according to the manufacturer recommendations (BD Biosciences or Pharmingen, San Diego, CA, USA).

Autoimmune complications were recorded for each patient. The diagnosis of autoimmunity was based on clinical and complementary paraclinical findings such as endoscopy, colonoscopy and biopsy results, laboratory tests, and radiologic studies based on international criteria (19). The measurement of an initial set of autoantibodies in our PIDs was evaluated where necessary. The evaluation of autoimmunity was reviewed by an immunologist and a subspecialist related to the affected organ or system.

IgG anti-thyroid peroxidase (TPO), IgG anti-thyroglobulin (Tg), and IgG thyroid-stimulating hormone receptor antibodies (TRAbs) for thyroid autoimmunity; IgA tissue transglutaminase antibodies, anti- endomysial, and anti-gliadin antibodies, anti-liver kidney microsomal (LKM), anti- gastric parietal cell (GPC), and anti-mitochondrial- M2 (AMA-M2) antibodies for gastrointestinal manifestations; insulin autoantibodies (IAA) and glutamic acid decarboxylase 65 (GAD65) antibodies for IDDM; RF and IgG anti-citrullinated protein antibodies (ACPA) for arthritis; anti- Sm, anti-dsDNA, anti-SSA/Ro, and anti-SSB/ La antibodies for SLE or SS; for complement deficiencies, classical (CH50) and alternative (AH50) complement functions were evaluated where necessary (20-23).

IIF detected antinuclear antibodies (ANA) with a HEp-2 ANA Complete Kit (IMMCO Diagnostics®, Buffalo, New York, USA). For all samples, the starting serum dilution was 1:160 titer. IIF detected antineutrophil cytoplasmic antibody (cytoplasmic and perinuclear patterns; cANCA and pANCA) with ANCA Complete Kit (IMMCO Diagnostics®, Buffalo, New York, USA). For all samples, the starting serum dilution was 1:40 titer. IIF detected LKM and GPC antibodies with a Mouse Kidney/Stomach/Liver Substrate Complete Kit (IMMCO Diagnostics®, Buffalo, New York, USA). For all samples, the starting serum dilution was 1:40 titer. IIF detected Crithidia luciliae immunofluorescence test (CLIFT) with Crithidia luciliae double-stranded DNA Antibody IgG Kit (IMMCO Diagnostics®, Buffalo, New York, USA). For all samples, the starting serum dilution was 1:10 titer.

ANA immunoblot test was evaluated using the EUROLINE ANA Profile 3 (EUROIMMUNE, Perkin Elmer Germany Diagnostics GmbH, Lübeck, Germany). Fifteen autoantibodies can be determined: Antibodies against RNP/Sm, Sm, SS-A, Ro-52, SS-B, Scl-70, PM-Scl, Jo-1, centromere protein B, PCNA, dsDNA, nucleosomes, histones, ribosomal P-proteins, AMA M2. For all samples, the cut-off value was 1:101 dilution. The ELISA method (EUROIMMUNE®, PerkinElmer Germany Diagnostics GmbH, Lübeck, Germany) was used to detect antibodies against dsDNA, AMA-M2, Rheumatoid factor (Rf), and ACPA. The cut-off value for AMA-M2 is <20 IU/mL, for ACPA is <5 IU/mL, for Rf <20 IU/mL, and for dsDNA is <100 IU/mL. Due to the hypogammaglobulinemia condition and defect in specific antibody response in patients with PID, a lower limit of positive results of autoantibody levels is considered significant for establishing the diagnosis of autoimmune diseases (19).

Statistical Analyses

Values were expressed as frequency (number and percentage), mean (range) as appropriate. Fisher's exact test and chi-square tests were used for 2 × 2 comparisons of categorical variables. Mann-Whitney U and Kruskal-Wallis H test was used to compare numerical variables, where the numbers were <30. Statistical analyses were performed using the SPSS software package, version 23 (SPSS Inc., Chicago, IL, USA). Results with $p<0.05$ were evaluated as statistically significant.

RESULTS

Baseline Demographic Data

In this retrospective study, 92 patients (50 males and 42 females) with PID were evaluated. Their mean age was 40.92 (18-86). Autoimmunity was evident in 29 patients (32%) (15 females and 14 males) with a mean age of 43.8 (19-78).

Baseline Laboratory Data

The routine complete blood count (CBC), blood immunoglobulin levels, and the results of the peripheral blood flow cytometric analyses of all patients are given in separate tables (Table I, II). The groups with and without

autoimmunity were compared with each other; CBC and blood immunoglobulin levels were similar among each group; however, in our PID group with ADs, Treg (T regulatory) cells and $CD21^{low}$ B cells were higher than the ones in the group of PIDs without autoimmunity. On the other hand, we found that the PIDs with AIDs had lower switched memory B cells and CD8 naive T cells than the group without ADs (Table II). When we compare the groups' parameters, no statical significant result was obtained (Table I, II).

Clinical Evaluation

Seventeen different types of PIDs were evaluated. CVID (n=60), IgM deficiency (n=7), CID (n=5), sIgAD (n=3), CTLA4 haploinsufficiency (n=3), MHC Class 1 deficiency

Table I. The results of the complete blood count and blood immunoglobulin levels of the PIDs at the time of diagnosis.

Parameter	PID+NI group (n=63) Median values (min-max)	PID+AD group (n=29) Median values (min-max)	Reference ranges*	p-value *
WBC (10^3 cell/ml)	5.93 (2.25-14.50)	6.55 (1.76-14.20)	4-10 x10^3 /ml	0.768
PNL (10^3 cell/ml)	3.86 (0.60-10.90)	3.41 (0.34-8.45)	1.5-7.3 x10^3 /ml	0.617
LYM (10^3 cell/ml)	1.53 (0.30-3.5)	1.81 (0.38-7.51)	0.8-5.5 x10^3 /ml	0.453
PLT (10^3 cell/ml)	217 (33-477)	206 (25-544)	150-400 x10^3 /ml	0.570
IgG (mg/dl)	300 (33.3-2170)	290 (34-1720)	650-1600 mg/dl	0.727
IgM (mg/dl)	25 (4-1040)	25 (14-374)	50-300 mg/dl	0.805
IgA (mg/dl)	84.36 (6-817)	50.5 (1-309)	40-350 mg/dl	0.658
IgG1 (mg/dl)	365 (4.67-1420)	392 (87.30-1390)	291-1000 mg/dl	0.654
IgG2 (mg/dl)	119 (0.97-1270)	140.5 (17.20-1160)	196-537 mg/dl	0.879
IgG3 (mg/dl)	18.80 (0.07-832)	22.70 (3-66.70)	24-124 mg/dl	0.916
IgG4 (mg/dl)	7 (0.16-365)	7.06 (0.1-55)	77-88 mg/dl	0.675

WBC: White blood cell; **PNL:** Neutrophil; **LYM:** Lymphocyte; **PLT:** Platelet; **PID:** Primary immune deficiency; **NI:** Non-autoimmunity; **AD:** Autoimmune disease; **Ig:** Immunoglobulin; **CD:** Cluster of differentiation. *p<0,05 is significant.* Referance ranges are referred (24-26).

Table II. The results of the peripheral blood flow cytometric analysis of all patients at the time of diagnosis.

Parameter	PID+NI group (n=63) Median values (min-max)	PID+AD group (n=29) Median values (min-max)	Reference ranges*	p-value *
CD3+ T cell, %	74 (32-92)	76 (39-94)	Male: 48-82.6 %; Female: 56.8-84.1%	0.70
CD4+ T cell, %	32 (7-69)	31 (10-66)	Male: 23-52.6 % ; Female: 26.9-55.5 %	0.934
CD8+ T cell, %	36 (10-78)	39 (8-71)	12.8-40.2 %	0.739
CD19+ B cell, %	9 (0-28)	8 (0-44)	12.8-40.2 %	0.993
CD3-16+56+ NK cell, %	8 (1-26)	6 (1-31)	Male: 5-31.3 %; Female: 3.5-24.9 %	0.330
IgM+D+CD27- B cell (naive B), %	87.45 (24.80-99)	90.50 (0-99)	43.2-82.4%	0.263
IgM-D-CD27+ B cell (switched memory B), %	**0.85 (0-44)**	**0.30 (0-40)**	6.5-29.2%	0.307
CD4+25+127- T cell (Treg), %	**0.25 (0-5.8)**	**0.85 (0-88)**	NA*	0.059
CD21-38- B cell ($CD21^{low}$), %	**3.4 (0.2-34)**	**6.3 (0-60)**	0.8-7.7%	0.107
CD4+45RA+CCR7+ T cell (naive CD4+), %	3 (0.3-59)	3.1 (0.1-68.5)	21-58%	0.965
CD8+ 45RA+CCR7+ T cell (naive CD8), %	**8.5 (0.1-76)**	**4.60 (0.1-75)**	5.7-10.3%	0.722

PID: primary immune deficiency; **NI:** non-autoimmunity; **AD:** autoimmune disease; **Ig:** immunoglobulin; **CD:** cluster of differentiation; **NA:** not available. *p<0,05 is significant. *The normal range of the Tregulatuar cells is not available. * Reference ranges are referred to (27).

(n=2), CGD (n=2), specific IgG subclass deficiency (n=1), APS (n=1), DC (n=1), Bruton agammaglobulinemia (n=1), X-linked agammaglobulinemia (n=1), GATA2 mutation (n=1), NBS (n=1), CHH (n=1), ORW (n=1), and GS (n=1) were detected.

CVID (n=17), CID (n=3), CTLA4 deficiency (n=2), sIgAD (n=2), IgG subgroup deficiency (n=1), APS (n=1), DC (n=1), ORW (n=1), and CHH (n=1) had ADs (Figure 1).

ADs were detected in 35.7% (15/42) of the female and 28% (14/50) of the male patients. No gender relation about ADs was observed in our cohort.

The frequency of ADs according to the systemic assessment resulted as endocrinologic diseases in 14% [7 AITD, 5 IDDM, one autoimmune Addison disease (AAD)], dermatologic diseases in 10.8% [4 CSU, 2 Alopecia Universalis, one vitiligo, one morphea, one nail dystrophy, one discoid lupus erythematosus (DLE)], rheumatologic diseases in 9.7% [1 uveitis, one rheumatoid like peripheral arthritis, one seronegative spondylitis, one unilateral sacroiliitis and peripheral arthritis, one ankylosing spondylitis (AS), 3 RA, 1 SS], gastroenterological diseases in 9.7% [6 CLE, 1 PA, 1 PBC, one primary sclerosing cholangitis (PSC)], hematologic diseases in 8.6% (5 ITP, 2 AIHA, 1 AIN), and neurologic system diseases in 1% (peripherical neuropathy) (Figure 2). The most common ADs in all patients were AITD (n=7), CLE (n=6), ITP (n=5) and IDDM (n=5).

We investigated the percentage of positivity rates for each type of PID; ADs were detected in 28.3% of CVID, 3 of 5 with CID, each of the 2 of 3 sIgAD and CTLA4 haploinsufficiency, and 1 of each with IgG subclass deficiency, DC, APS, CHH, and ORW. The frequency of ADs was higher in CVID (58.6 %) than other types of PID ($p < 0.05$).

Among 17 CVID, dermatologic (n=6) (4 CSU, 1 vitiligo, 1 DLE), endocrinologic (n=5) (4 AITD, 1 IDDM), rheumatologic (n=4) (1 seronegative spondylitis, 2 RA, 1 rheumatoid like peripheral arthritis, 1 SS), hematologic (n=4) (2 ITP, 1 AIHA, 1 AIN), gastroenterologic (n=3) (2 CLE, 1 PSC), and neurologic ADs (n=1) (peripherical neuropathy) were detected.

While 17.3% (n=16) of the patients had only one type of AD, 14 % (n=13) had overlapped ADs. Multiple ADs were detected in seven males and six females, and multiple ADs were not related to gender. PIDs presenting with multiple ADs were CVID (n=7), CTLA-4 deficiency (n=2), and 1 of each with ORW, APS, DC, and sIgAD.

Among 29 patients with autoimmune manifestations, 9 (Table III; P1, 2, 7, 9, 15, 22, 25, 26, 29) had rheumatologic ADs. Nevertheless, only two (22%) had autoantibodies related to their ADs (Table III, P7, 22). The co-occurrence of rheumatologic and non-rheumatologic autoimmune manifestations was reported in 7 patients (Table III; P1, 2, 7, 9, 15, 22, 29) (gastroenterologic in 3, hematologic in 2, endocrinologic in 4, dermatologic in 2).

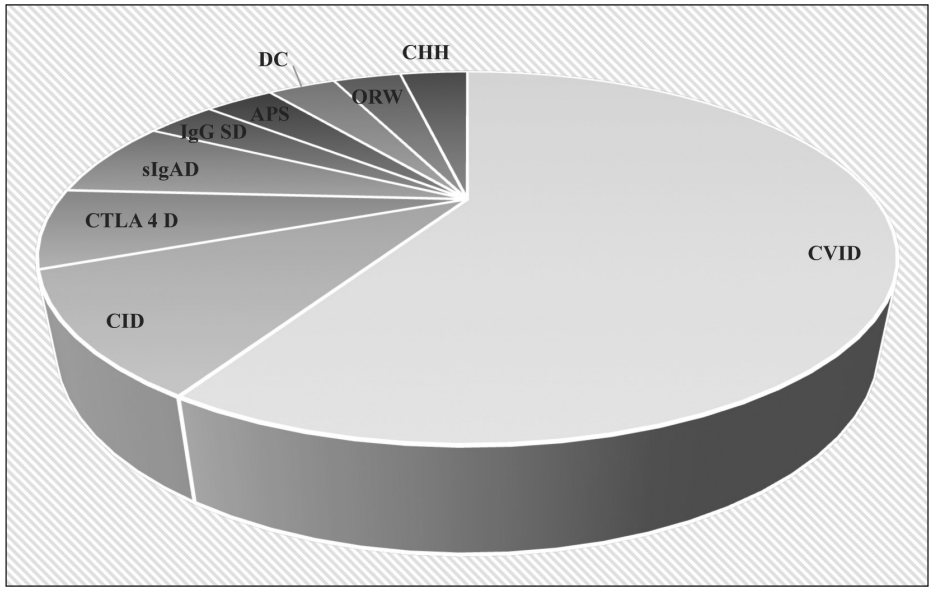

Figure 1. The distribution of the PIDs with ADs.

CVID: *Çommon variable immune deficiency;* ***CID:*** *Combined immune deficiency;* ***CTLA4 D:*** *CTLA4 Deficiency;* ***sIgAD:*** *Selective IgA deficiency;* ***IgG SD:*** *IgG subgroup deficiency;* ***APS:*** *Autoimmune Polyglandular Syndrome with hypogammaglobulinemia;* ***DC:*** *Dyskeratosis Congenita;* ***ORW:*** *Osler-Rendu-Weber syndrome with CVID-like PID;* ***CHH:*** *Cartilage-Hair Hypoplasia.*

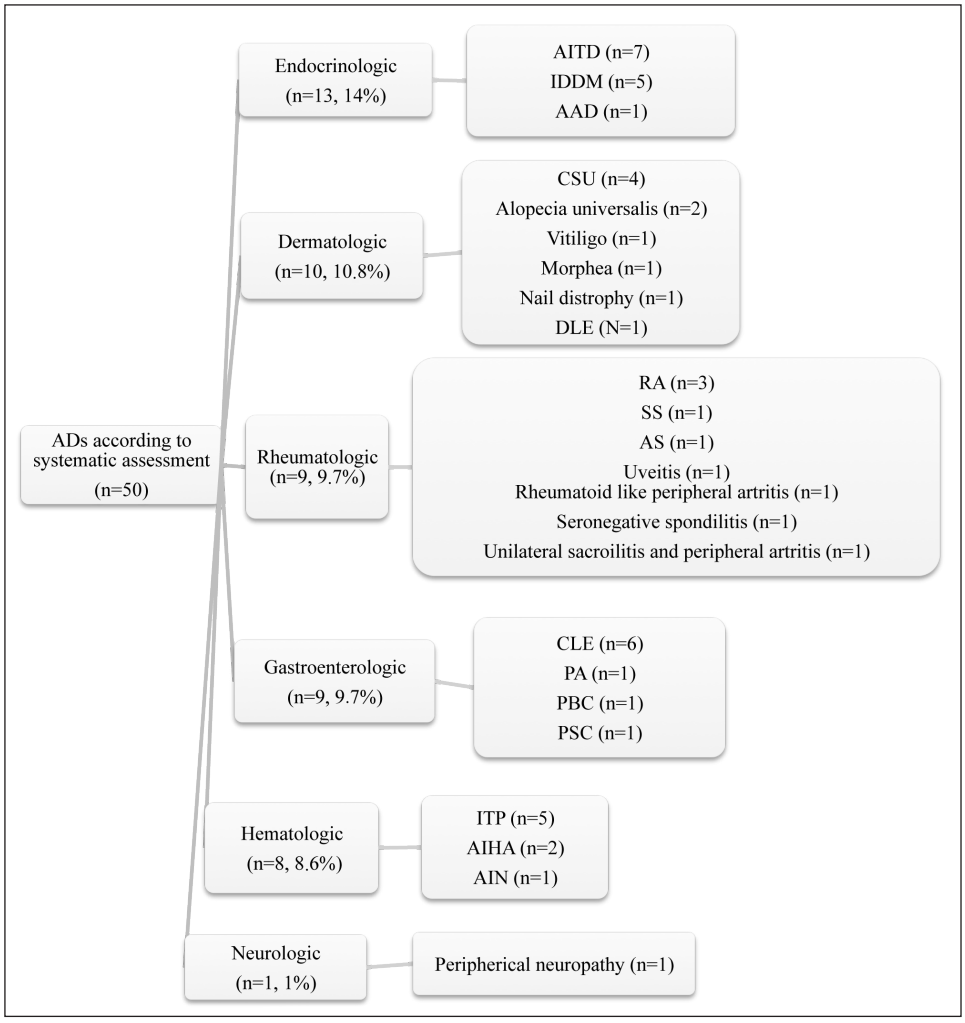

Figure 2. The classification of the ADs according to the systematic assessment in our PID group.

AD: *autoimmune disease;* ***AITD:*** *autoimmune thyroid disease;* ***IDDM:*** *insulin-dependent diabetes mellitus;* ***AAD:*** *autoimmune Addison disease;* ***CSU:*** *chronic spontaneous urticaria;* ***DLE:*** *discoid lupus erythematosus;* ***RA:*** *rheumatoid arthritis;* ***SS:*** *Sjogren's syndrome;* ***AS:*** *ankylosing spondylitis;* ***CLE:*** *celiac-like enteropathy;* ***PA:*** *pernicious anemia;* ***PBC:*** *primary biliary cirrhosis;* ***PSC:*** *primary sclerosing cholangitis;* ***ITP:*** *idiopathic thrombocytopenic purpura;* ***AIHA:*** *autoimmune hemolytic anemia;* ***AIN:*** *autoimmune neutropenia.*

Among our 29 PIDs with autoimmunity, 12 had autoantibodies (eight males, four females); ANA in six (two with CVID, and one of each with APS, IgA deficiency, IgG subgroup deficiency, and CID); LKM antibody in five (three with CVID, and one of each with CID and CTLA4 haploinsufficiency), and TPO/Tg antibody was detected in 14 patients as the most common autoantibodies. ANA was detected in one CSU, one SS, and one APS (Table III; P10, 21, 22), TPO and Tg antibody were in 2 AITD (Table III; P3, P18), and GPC antibody was in one CTLA4 haploinsufficiency with multiple ADs (Table III; P7). Among 92 cases of PID, ten patients (9.2%) had autoantibodies without clinical data of an AD. Those antibodies were both ANA and GPC positivity in 1, GPC in 1, the anti-ribosomal antibody in 1, and the TPO antibody in 7 patients.

In our PID cohort, 66 patients (71.7%) were administered intravenous immunoglobulin (IVIG), 16 (17.3%) were switched from IVIG to subcutaneous immunoglobulin (SCIG) therapy, and the rest of the patients (n=10, 11%) [sIgAD (n=3), IgM and IgG subgroup deficiency (n=7)] were followed-up regularly with blood immunoglobulin levels approximately every six months at the outpatient clinic. The median dose of the immunoglobulin replacement was 600 mg/kg/3 weeks (min: 400, max: 800 mg/kg/3 weeks) for IVIG and 133 mg/kg/week (83.3-266.3 mg/kg/week) for SCIG.

In addition specific therapy was administered for each of the autoimmune complications. PIDs with CTLA4 deficiency were treated with abatacept IV/SC; peroral/parenteral hormone replacement was given regularly for endocrinologic autoimmunities; parenteral/enteral replacement of vitamins and/or minerals were administered

Table III. Detailed features of PIDs with ADs.

Patient	Sex	Age	Type of PID	AD	Autoantibody
1	M	31	CTLA4 haploinsuffiency	IDDM, uveitis, ITP	Negative
2	M	33	CVID	CLE, seronegative spondylitis	Negative
3	F	21	sIgAD	AITD	**ANA (granular 1/320 +, anti-Scl 2+, DFS70 3+), anti-TPO**
4	F	45	IgG subclass deficiency	AITD	Negative
5	F	78	CVID	CSU	Negative
6	M	35	sIgAD	IDDM, vitiligo, PA	Negative
7	M	25	CTLA4 haploinsufficiency	IDDM, ITP, AAD, CLE, unilateral sacroiliitis and peripheral arthritis, alopecia universalis, nail dystrophy	**Anti-GPC 1/20+**
8	F	59	CVID	AITD	Negative
9	F	41	DC	Vitiligo, RA	**Anti-TPO, Anti-Tg**
10	F	19	APS	IDDM, CLE, morphea, AAD, alopecia universalis, AITD, retinitis pigmentosa	**ANA (lamin 1/160+ cytoplasmic 1/160, DFS70 3+)**
11	F	41	CVID	CLE	Negative
12	F	52	CID	CLE	Negative
13	M	73	CVID	ITP	**Anti-TPO**
14	F	67	CVID	CSU	Negative
15	F	49	CVID	AITD, rheumatoid- like peripheral arthritis	Negative
16	M	27	CVID	ITP, DLE	Negative
17	M	58	CVID	Peripherical neuropathy	**Anti - GPC 1/80 +**
18	M	47	CVID	AITD	**Anti-TPO, Anti- Tg**
19	M	41	CHH	PBC	Negative
20	M	24	ORW	AIHA, ITP	Negative
21	M	29	CVID	CSU	**ANA (granular 1/320 +, DFS70 3+)**
22	F	60	CVID	SS, AITD	**ANA (centromeric 1/80 +)**
23	F	45	CVID	Vitiligo, CSU	Negative
24	F	37	CVID	AIHA, AIN, AITD	Negative
25	M	55	CVID	RA	**Anti-TPO**
26	M	31	CID	AS	**Anti-TPO**
27	F	34	CVID	IDDM	Negative
28	F	55	CID	CLE	Negative
29	M	61	CVID	PSC, RA	**Anti-TPO**

PID: Primary immune deficiency; **AD:** Autoimmune disease; **CVID:** Common variable immune deficiency; **CID:** Combined immune deficiency; **sIgAD:** Selective IgA deficiency; **APS:** Autoimmune Polyglandular Syndrome with hypogammaglobulinemia; **DC:** Dyskeratosis Congenita; **CHH:** Cartilage-Hair Hypoplasia; **ORW:** Osler-Rendu-Weber syndrome with CVID-like PID; **ANA:** Antinuclear antibody; **IDDM:** Insulin-dependent diabetes mellitus; **CLE:** Celiac-like enteropathy; **AITD:** Autoimmune thyroid disease; **PA:** Pernicious anemia; **AAD:** Autoimmune Addison disease; **RA:** Rheumatoid arthritis; **DLE:** Discoid lupus erythematosus; **PBC:** Primary biliary cirrhosis; **SS:** Sjogren's syndrome; **AIHA:** Autoimmune hemolytic anemia; **AIN:** Autoimmune neutropenia; **PSC:** Primary sclerosing cholangitis, **CSU:** Chronic spontaneous urticaria.

where necessary; biological agents were administered as rituximab for ITP, omalizumab for CSU, ustekinumab for enteropathy; immunosuppressive and immunomodulators (corticosteroids, azathioprine, methotrexate, sulfasalazine, sirolimus, everolimus, and ursodeoxycholic acid) were administered for rheumatic, dermatologic, hematologic and gastroenterological ADs.

During the follow-up, 3 PIDs with ADs developed malignant neoplasm (diffuse large B-cell lymphoma, large granular lymphocytic leukemia/lymphoma), and 2 PIDs without ADs developed malignant neoplasm (non-Hodgkin lymphoma and gastric adenocarcinoma). All of the PIDs with malign neoplasms died due to those malignities. The patient with GATA2 deficiency had allogeneic bone marrow transplantation, but afterward, the patient died due to infections; seven patients (5 PIDs without ADs, one PID with AD, and one GATA2 deficiency) died due to the infectious complications. One of our PIDs with ADs, who had liver transplantation due to autoimmune hepatitis, died due to liver bleeding.

DISCUSSION

In this study, we conducted a retrospective, cross-sectional analysis of ADs and related laboratory findings in a well-defined cohort of 92 patients with 17 different PIDs.

PIDs are susceptible to ADs, mainly because, their central and peripheral tolerance of the adaptive immune system is defective (1, 11-16). As a result, the uncleansable antigens eventuate in the occurrence of the immune complexes in end-organs, activation of the immune cells, generation of the chronic inflammation, and composition of the anti-tissue antibodies, so that, tissue destruction is observed (11, 23, 28-33).

Kilic et al. analyzed the distribution of PIDs in Turkey. Primary antibody immunodeficiency (PAD) (73.5%) was the most common category, followed by autoinflammatory disorders (13.3%), other well-defined immunodeficiencies (5.5%), congenital defects of phagocyte number, function, or both (3.5%), combined T and B cell immunodeficiencies (2%), defects in innate immunity (1%); and diseases of immune dysregulation (0.7%), as similar to the distribution of our cohort (34).

ADs may be the first manifestation of PID. The prevalence of ADs in sIgAD is reported as 36% (35), in CVID as 20-30% (36), and in Wiskott-Aldrich syndrome as 25% (37,38). The rate of ADs in our cohort was 32%, which is slightly more than the rate mentioned in the literature (39).

In the DEFI study, the rate of patients with autoimmune conditions at first admission was 10%. In the same study, the autoimmune cytopenia rate during follow-up was reported as 18% (40). In the study by Aytekin et al., 36.8% of the 47 CVID patients developed autoimmune complications, and 29.8% had autoimmune cytopenia (41). Their results are similar to the previous literature, but different from ours' because we report the endocrinologic autoimmunities as the most common.

In our PID cohort, the most common autoimmunities were related to endocrinologic (14%), dermatologic (10.8%), hematologic (9.7%), and gastroenterologic systems (9.7%). The most common diseases were found as AITD (n=7), CLE (n=6), ITP (n=5), and IDDM (n=5). In the study by Blazina et al., 247 patients with 50 different PIDs were evaluated, and 22% of PID patients developed an AD. ADs were diagnosed in 47% of patients with CGD and 38% of PAD (39). The most common ADs observed in their study were enteropathy, JIA/RA, dermatitis, AITD, and cytopenia, like our results. In our PID cohort, we detected ADs in 2 of 3 cases with sIgAD, which was higher than in the PID cohort of Blazina et al., where ADs were diagnosed in 42% of sIgADs (39). Also, 2 of 3 cases with CTLA-4 deficiency had ADs and especially, their first presentation was ADs.

ADs may be the presenting or only symptom for CVID (6, 42-44). The most commonly reported autoimmune conditions in CVID are hematologic (25-30%) (ITP, AIHA, and AIN), rheumatologic (RA/JRA) (1-10%), gastroenterologic (CLE) (6-10%), and liver diseases (PBC, autoimmune hepatitis, and PA) (1-9%) (6-8, 43-47). In our cohort, among 60 patients with CVID, 29% (n=17) had ADs, and the most common ADs are autoimmune cytopenias, AITD, and CSU. Our prevalence is compatible with the one in the literature where the prevalence of ADs in CVID is reported as 20-30% (39, 41-47). In the two different studies by Azizi et al., ADs were recorded in 26.5% of PAD patients, and the frequency of autoimmunity was higher in CVID than other kinds of PADs (45, 46). Gastroenterological, hematologic, and rheumatologic disorders were the most frequent autoimmune complications (48). According to Blazina et al., Resnick et

al., and Boileau J et al., the prevalence of autoimmunity in CVID was 31%, 29%, and 40.3% of PADs, respectively (39, 40, 47).

In our study, among all of the PIDs, the female to male ratio was 1 to 1.1. Oksenhendler et al. reported that 56.3% of the patients were female, and 43.7% were male (49). In a study evaluating 2212 CVID patients, 51.1% were female, and 48.9% were male (50). According to the previously published literature from Turkey, Ardeniz et al. reported a female to male ratio of 1 to 1.3 (51), and Muşabak et al. reported this ratio as 1 to 1.6 (52). In the study by Aytekin et al. (41), a female to male ratio of 1 to 1.1 was reported, similar to our result and the previously published articles.

ADs are observed in approximately 8% of the general population, however, they occur mostly in female patients (~ 80%). In our PID cohort, we found the prevalence of autoimmunity higher than the approximate prevalence of ADs in general. Also, we observed no sex predominance among our patients with ADs (15 female:14 male) in contrast to the normal population. The studies which were performed in a population with an intact immune system showed that SS and AITD are mostly related to sex (the female: the male is 7:1-10:1). In RA, sex bias could also be mentioned (the female: the male is 2:1-3:1), but, no sex relation is observed in IBD, ITP, and IDDM. In our cohort, the most common ADs are AITD, CLE, ITP, and IDDM. We have a higher male rate; this is thought to be related to the result of the lower ratio of sex associated ADs (45, 53-58).

It was reported that about 25% of patients with ADs tend to develop other ADs (59). In our study among PID patients with autoimmunity, 14% had multiple ADs. Another critical point of our results is the frequency of autoantibody positivity among our PIDs with ADs was 41%. This result shows that the presence of autoantibodies for ADs in PID is possible but not necessary. On the other hand, ANA could be positive in the normal population with lower titers than 1:160. As seen from our data, 9.2 % of PIDs had ANA positivity with no data of ADs. That is why we should have certain proofs while diagnosing ADs in an ANA-positive patient.

In the published literature by Warnatz K. et al., decreased switched memory B cells and increased $CD21^{low}$ B cells are related more to autoimmune cytopenias (60). Fevang et al. and Arumugakani et al. showed that the Treg and CD8 T cells' decreases are associated with increased frequency of ADs (61, 62). In the study by Boileau et al., where blood IgG levels and $CD21^{low}$ B cells were found increased, naive CD4 T cells were decreased in the autoimmune cytopenia group, when compared with the non-autoimmunity group (40). On the other hand, similar to our results, they confirmed that B and T cell abnormalities detected in autoimmune cytopenia are specific to the disease itself, without any relation to the other autoimmune manifestations (40).

The incidence of non-Hodgkin lymphoma increases significantly in CVID patients. Cunningham-Rundles et al. reported that the risk of lymphoma in female CVID patients was 478-fold higher than in a similar age group (63). In a study by Ardeniz et al., lymphoma developed in three out of 23 patients during the follow-up (51). In another study from Turkey by Aytekin et al., malignancy developed in 3 patients during the follow-up, and all of them were non-Hodgkin lymphoma (41). Among our PID group, malignancy was detected in 5 patients during the follow-up, 4 of them were lymphomas (diffuse large B-cell lymphoma, large granular lymphocytic leukemia/ lymphoma, non-Hodgkin lymphoma), and 1 was solid malignancy (gastric adenocarcinoma).

Finally, this research is a retrospective study and so has the limitations of this design; for example, different distribution of autoimmune complications in various PIDs might be present, and some of our findings, like endocrinologic autoimmunities as the most common type of ADs, could be different from the literature data.

CONCLUSION

The result of the current study contributes to our understanding of ADs in different types of PIDs and is potentially valuable in managing patients. ADs can help physicians to make the diagnosis of PID. Non-immunologist physicians should be alert to associate ADs with the underlying PID to reduce the diagnostic delay. In the current literature, most of the studies lack the knowledge about the spectrum of ADs in PIDs or they give information only about a specific type of PID. Our results are important as we add new information to the preceding literature data about the ADs diagnosed in the different spectrum of PIDs.

REFERENCES

1. Schmidt RE, Grimbacher B, Witte T. Autoimmunity and primary immunodeficiency: Two sides of the same coin? Nat Rev Rheumatol 2017;14(1):7-18.
2. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol 2018;38(1):96-128.
3. Lugo Reyes SO, Ramirez-Vazquez G, Cruz Hernández A, Medina-Torres EA, Ramirez-Lopez AB, España-Cabrera C, et al. Clinical features, non-infectious manifestations and survival analysis of 161 children with primary immunodeficiency in Mexico: A single center experience over two decades. J Clin Immunol 2016;36(1):56-65.
4. Aghamohammadi A, Mohammadinejad P, Abolhassani H, Mirminachi B, Movahedi M, Gharagozlou M, et al. Primary immunodeficiency disorders in Iran: Update and new insights from the third report of the national registry. J Clin Immunol 2014;34(4):478-90.
5. Yazdani R, Latif A, Tabassomi F, Abolhassani H, Azizi G, Rezaei N, et al. Clinical phenotype classification for selective immunoglobulin A deficiency. Expert Rev Clin Immunol 2015;11(11):1245-54.
6. Azizi G, Abolhassani H, Asgardoon MH, Alinia T, Yazdani R, Mohammadi J, et al. Autoimmunity in common variable immunodeficiency: Epidemiology, pathophysiology and management. Expert Rev Clin Immunol 2017;13(2):101-15.
7. Brandt D, Gershwin ME. Common variable immune deficiency and autoimmunity. Autoimmun Rev 2006;5: 465-70.
8. Knight AK, Cunningham-Rundles C. Inflammatory and autoimmune complications of common variable immune deficiency. Autoimmun Rev 2006;5:156-9.
9. Bussone G, Mouthon L. Autoimmune manifestations in primary immune deficiencies. Autoimmun Rev 2009;8(4):332-6.
10. Haymore BR, Mikita CP, Tsokos GC. Common variable immune deficiency (CVID) presenting as an autoimmune disease: The role of memory B cells. Autoimmun Rev 2008; 7: 309-12.
11. Azizi G, Ziaee V, Tavakol M, Alinia T, Yazdai R, Mohammadi H, et al. Approach to the management of autoimmunity in primary immunodeficiency. Scand J Immunol 2017;85(1):13-29.
12. Arason GJ, Jorgensen GH, Ludviksson BR. Primary immunodeficiency and autoimmunity: Lessons from human diseases. Scand J Immunol 2010;71(5):317-28.
13. Atkinson TP. Immune deficiency and autoimmunity. Curr Opin Rheumatol 2012;24(5):515-21.
14. Sharfe N, Merico D, Karanxha A, Macdonald C, Dadi H, Ngan B, et al. The effects of RelB deficiency on lymphocyte development and function. J Autoimmun 2015;65: 90-100.
15. Arandi N, Mirshafiey A, Jeddi-Tehrani M, Shaghaghi M, Sadeghi B, Abolhassani H, et al. Alteration in frequency and function of CD4(+)CD25(+)FOXP3(+) regulatory T cells in patients with immune thrombocytopenic purpura. Iran J Allergy Asthma Immunol 2014;13(2):85-92.
16. Arandi N, Mirshafiey A, Jeddi-Tehrani M, Abolhassani H, Sadeghi B, Mirminachi B, et al. Evaluation of CD4+CD25+FOXP3+ regulatory T cells function in patients with common variable immunodeficiency. Cell Immunol 2013;281(2):129-33.
17. European Societies for Immunodeficiencies. 2017. Clinical diagnostic criteria for PID. Available from: https://esid.org/Working-Parties/ Clinical/Resources/Diagnostic-criteria-for-PID
18. Yazdani R, Ganjalikhani-Hakemi M, Esmaeili M, Abolhassani H, Vaeli S, Rezaei A, et al. Impaired Akt phosphorylation in B-cells of patients with common variable immunodeficiency. Clin Immunol 2017;175:124-32.
19. Shoenfeld Y, Cervera R, Gershwin ME, editors. Diagnostic criteria in autoimmune diseases. Humana Press, Springer Science Business Media, LLC; 2008.
20. Karaoglu A, Sarı E, Yeşilkaya E. Hashimoto's Thyroiditis in Children and Adolescents, Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights, Fang-Ping Huang, IntechOpen.
21. Léger J, Kaguelidou F, Alberti C, Carel JC. Graves' disease in children. Best Pract Res Clin Endocrinol Metab 2014;28(2):233-43.
22. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2019. American Diabetes Association. Diabetes Care 2019;42 (Supplement 1):S13-S28.
23. Bousfiha A, Jeddane L, Picard C, Ailal F, Bobby Gaspar H, Al-Herz W, et al. The 2017 IUIS Phenotypic classification for primary immunodeficiencies. J Clin Immunol 2018;38(1):129-43.
24. Hollowell JG, van Assendelft OW, Gunter EW, Lewis BG, Najjar M, Pfeiffer C; Centers for Disease Control and Prevention, National Center for Health Statistics. Hematological and iron-related analytes--reference data for persons aged 1 year and over: United States, 1988-94. Vital Health Stat 11 2005;(247):1-156.
25. Valent P. Low blood counts: Immune-mediated, idiopathic, or myelodysplasia. Hematology Am Soc Hematol Educ Program 2012; 2012:485-91.
26. Ameratunga R, Woon ST, Gillis D, Koopmans W, Steele R. New diagnostic criteria for common variable immune deficiency (CVID), which may assist with decisions to treat with intravenous or subcutaneous immunoglobulin. Clin Exp Immunol 2013;174(2):203-11.
27. Rudolf-Oliveira RC, Goncalves KT, Martignago ML, Mengatto V, Gaspar PC, de Moraes AC, et al. Determination of lymphocyte subset reference ranges in peripheral blood of healthy adults by a dual-platform flow cytometry method. Immunol Lett 2015;163(1):96-101.
28. Melki I, Crow YJ. Novel monogenic diseases causing human autoimmunity. Curr Opin Immunol 2015;37:1-5.
29. Westerberg LS, Klein C, Snapper SB. Breakdown of T cell tolerance and autoimmunity in primary immunodeficiency--lessons learned from monogenic disorders in mice and men. Curr Opin Immunol 2008;20(6):646-54.

30. Azizi G, Pouyani MR, Abolhassani H, Sharifi L, Dizaji MZ, Mohammadi J, et al. Cellular and molecular mechanisms of immune dysregulation and autoimmunity. Cell Immunol 2016;310:14-26.
31. Fairweather D, Kaya Z, Shellam GR, Lawson CM, Rose NR. From infection to autoimmunity. J Autoimmun 2001;16(3):175-86.
32. Panoutsakopoulou V, Cantor H. On the relationship between viral infection and autoimmunity. J Autoimmun 2001;16(3):341-5.
33. Arkwright PD, Abinun M, Cant AJ. Autoimmunity in human primary immunodeficiency diseases. Blood 2002;99(8):2694-702.
34. Kilic SS, Ozel M, Hafizoglu D, Karaca NE, Aksu G, Kutukculer N. The prevalences [correction] and patient characteristics of primary immunodeficiency diseases in Turkey--two centers study. J Clin Immunol 2013; 33(1):74-83.
35. Singh K, Chang C, Gershwin ME. IgA deficiency and autoimmunity. Autoimmun Rev 2014;13(2):163-77.
36. Patuzzo G, Barbieri A, Tinazzi E, Veneri D, Argentino G, Moretta F, et al. Autoimmunity and infection in common variable immunodeficiency (CVID). Autoimmun Rev 2016;15(9):877-82.
37. Schurman SH, Candotti F. Autoimmunity in Wiskott-Aldrich syndrome. Curr Opin Rheumatol 2003;15(4):446-53.
38. Ramenghi U, Bonissoni S, Migliaretti G, DeFranco S, Bottarel F, Gambaruto C, et al. Deficiency of the Fas apoptosis pathway without Fas gene mutations is a familial trait predisposing to development of autoimmune diseases and cancer. Blood 2000;95(10):3176-82.
39. Blazina S, Markelj G, Jeverica AK, Toplak N, Bratanič N, Jazbec J, et al. Autoimmune and inflammatory manifestations in 247 patients with primary immunodeficiency-a report from the Slovenian National Registry. J ClinImmunol 2016;36: 764-73.
40. Boileau J, Mouillot G, Gérard L, Carmagnat M, Rabian C, Oksenhendler E, et al; DEFI Study Group. Autoimmunity in common variable immunodeficiency: Correlation with lymphocyte phenotype in the French DEFI study. J Autoimmun 2011;36(1):25-32.
41. Aytekin G, Yıldız E, Çölkesen F, Arslan Ş, Çalışkaner AZ. Five years of experience in a single center: Retrospective analysis of adult patients with common variable immunodeficiency. Asthma Allergy Immunol 2020;18:30-7.
42. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol 2007;27(3):308-16.
43. Todoric K, Koontz JB, Mattox D, Tarrant TK. Autoimmunity in immunodeficiency. Curr Allergy Asthma Rep 2013;13: 361-70.
44. Azizi G, Ahmadi M, Abolhassani H, Yazdani R, Mohammadi H, Mirshafiey A, et al. Autoimmunity in primary antibody deficiencies. Int Arch Allergy Immunol 2016;171:180-93.
45. Azizi G, Tavakol M, Rafiemanesh H, Kiaee F, Yazdani R, Heydari A, et al. Autoimmunity in a cohort of 471 patients with primary antibody deficiencies. Expert Rev Clin Immunol 2017;13(11):1099-106.
46. Azizi G, Bagheri Y, Tavakol M, Askarimoghaddam F, Porrostami K, Rafiemanesh H, et al. The clinical and immunological features of patients with primary antibody deficiencies. Endocr Metab Immune Disord Drug Targets 2018; 18(5):537-45.
47. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012; 119:1650-7.
48. Azizi G, Kiaee F, Hedayat E, Yazdani R, Dolatshahi E, Alinia T, et al. Rheumatologic complications in a cohort of 227 patients with common variable immunodeficiency. Scand J Immunol 2018;87(5):e12663.
49. Oksenhendler E, Gerard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, et al, for the DEFI Study Group. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis 2008;46: 1547-54.
50. Gathmann B, Mahlaoui N, Ceredih, Gerard L, Oksenhendler E, Warnatz K, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol 2014;134(1):116-26.
51. Ardeniz O, Basoglu OK, Gunsar F, Unsel M, Bayraktaroglu S, Mete N, et al. Clinical and immunological analysis of 23 adult patients with common variable immunodeficiency. J Investig Allergol Clin Immunol 2010;20(3):222-36.
52. Muşabak UH, Demirel F, Yesillik S, Baysan A, Selcuk A, Kartal O, et al. Adults with common variable immunodeficiency: A single-center experience. Turk J Med Sci 2017;47(1):1-12.
53. Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. Am J Pathol 2008;173:600-9.
54. Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: Improved prevalence estimates and understanding of clustering of diseases. J Autoimmun 2009; 33: 197-207.
55. Abolhassani H, Gharib B, Shahinpour S, Masoom SN, Havaei A, Mirminachi B, et al. Autoimmunity in patients with selective IgA deficiency. J Invest Allergol Clin Immunol 2015;25:112-9.
56. Abolhassani H, Amirkashani D, Parvaneh N, Mohammadinejad P, Gharib B, Shahinpour S, et al. Autoimmune phenotype in patients with common variable immunodeficiency. J Invest Allergol Clin Immunol 2013; 23: 323-9.
57. Ortona E, Pierdominici M, Maselli A, Veroni C, Aloisi F, Shoenfeld Y. Sex-based differences in autoimmune diseases. Annali dell'Istituto Superiore Di Sanita 2016;52: 205-12.
58. Saeidi S, Jaseb K, Asnafi AA, Rahim F, Pourmotahari F, Mardaniyan S, et al. Immune thrombocytopenic purpura in children and adults: A comparative retrospective study in Iran. Int J Hematol-Oncol Stem Cell Res 2014;8: 30-6.
59. Cojocaru M, Cojocaru IM, Silosi I. Multiple autoimmune syndrome. Maedica 2010;5: 132-4.

60. Warnatz K, Wehr C, Drager R, Schmidt S, Eibel H, Schlesier M, et al. Expansion of CD19hiCD21lo/neg B cells in common variable immunodeficiency (CVID) patients with autoimmune cytopenia. Immunobiology 2002;206:502-13.
61. Fevang B, Yndestad A, Sandberg WJ, Holm AM, Müller F, Aukrust P, et al. Low numbers of regulatory T cells in common variable immunodeficiency: Association with chronic inflammation in vivo. Clin Exp Immunol 2007;147:521-5.
62. Arumugakani G, Wood PMD, Carter CRD. Frequency of Treg cells is reduced in CVID patients with autoimmunity and splenomegaly and is associated with expanded CD21lo B lymphocytes. J Clin Immunol 2009;30:292-300.
63. Cunningham-Rundles C, Siegal FP, Cunningham-Rundles S, Lieberman P. Incidence of cancer in 98 patients with common varied immunodeficiency. J Clin Immunol 1987;7(4):294-9.