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Comparison of clinical and immunological features and mortality in common variable immunodeficiency and agammaglobulinemia patients

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ABSTRACT

Common Variable Immunodeficiency (CVID) and agammaglobulinemia are two of the main types of symptomatic primary antibody deficiencies. The pathogenic origins of these two diseases are different; agammaglobulinemia is a group of inherited disorders that usually are caused by mutations in the gene encoding Bruton Tyrosine Kinase (BTK) protein while CVID is a heterogeneous disorder mainly without monogenic cause. However, both diseases share a characteristic of frequent bacterial infections, a decline in serum immunoglobulin levels, and abnormality in antibody responses.

The demographics and immunologic parameters, clinical manifestation, and mortality statistics from 297 patients with CVID and agammaglobulinemia followed up over 2 decades in the Children's Medical Center of Iran.

Age at onset of symptom in agammaglobulinemia was earlier than CVID but the course of disease in CVID patients was longer than agammaglobulinemia patients. Pulmonary infections were the most prevalent clinical manifestations in both groups of patients. Lymphadenopathy, hepatomegaly, and splenomegaly were significantly higher in CVID patients than agammaglobulinemia patients and there was a significant association between these complications and mortality in CVID patients. Among 297 patients, 128 patients (88 CVID and 40 agammaglobulinemia) deceased. The predominant causes of death in CVID patients were infections, chronic lung disease, and malignancy while in agammaglobulinemia patients were infections and respiratory failure.

Infections, especially respiratory infections were the most common complication and cause of death in both CVID and agammaglobulinemia groups and recent treatment advances even Immunoglobulin replacement cannot completely control these complications. Thus prompt recognition and specific management of these complications are worthwhile.

1. Introduction

Primary Antibody Deficiency (PAD) is the main group of inherited immune disorders, resulting from B-cell lineage dysfunction or developmental arrest [1,2]. Agammaglobulinemia and Common Variable Immunodeficiency (CVID) are two of the major types of symptomatic

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PADs. Agammaglobulinemia is characterized by an early block of B cell development in the bone marrow, leading to the absence of peripheral B cells and low serum levels of all immunoglobulin (Ig) isotypes [3–5]. Mutations of *BTK*, which is the responsible gene for X-linked agammaglobulinemia (XLA), account for ~85% of cases with agammaglobulinemia [6]. The remaining 15% of patients constitute a heterogeneous group, including patients with mutations in *IGHM, IGLL1, CD79A, CD79B,* and *BLNK*, which are the genes responsible for the autosomal recessive forms of agammaglobulinemia. Autosomal recessive agammaglobulinemia is reported to show a more severe and early onset when compared to XLA [7,8]. CVID constitutes a heterogeneous group of PAD characterized by hypogammaglobulinemia and poor to absent specific antibody responses to protein and/or polysaccharide antigens [1,9–11]. Various single gene defects have been described in patients presenting with clinical features of CVID over the recent years [11,12] and the list is still expanding. However, the pathogenic etiology remained unknown in the majority of patients.

These patients are susceptible to recurrent bacterial infections, mainly the respiratory and gastrointestinal (GI) tracts; while a number of non-infectious complications, including autoimmunity, interstitial lung disease, granulomatous disease, enteropathy, lymphoid hyperplasia, and lymphoma and/or other cancers are prevalent in these disorders [13–15]. Following up 473 patients with CVID over 4 decades showed that 94% of patients had a history of infections and 68% also had noninfectious complications. In addition, the risk of death was 11 times higher for patients with noninfectious complications [16,17]. Twenty to thirty percent of the patients with CVID develop autoimmune manifestations [18]; in contrast, patients with XLA are spared these complications [19]. In our previous study, we estimated that post-diagnosis survival of CVID patients as 65% for the first 6.5 years, which remains the same until 14 years after diagnosis when the survival curve drops to nearly 45% [17]. In contrast, we observed individually that 26.8% of XLA patients died during the 20 follow-up period [20]. Compared with XLA patients, patients with CVID have a greater likelihood of developing lung disease, possibly due to delayed diagnosis and immune dysregulation [13]. The aim of this study is to evaluate the detailed clinical and immunological phenotypes of Iranian patients with agammaglobulinemia and CVID in accordance with morbidities and mortality rate in the past twenty years and compare the findings of these two diseases to each other.

2. Patients and methods

2.1. Patients

The Immunodeficiency Clinic at the Children's Medical Center affiliated to Tehran University of Medical Sciences is a referral center for primary immunodeficiency diseases [21]. A total of 297 (CVID = 195 and agammaglobulinemia = 102) patients, who were diagnosed and treated at this center between 1995 and 2016, were entered into this study. The diagnosis of CVID or agammaglobulinemia was re-evaluated according to the criteria of the European Society for Immunodeficiencies (ESID, https://esid.org/Working-Parties/Registry/Diagnosis-criteria). CVID was diagnosed based on hypogammaglobulinemia 2 standard deviations (SD) lower than normal range for age, defect in specific antibody response, recurrent and severe infections, age older than 4 years (to exclude the probability of transient hypogammaglobulinemia), no evidence of profound T-cell deficiency and no other cause identified for the immune defect. Of note, in patients that alive and available in 2017 the diagnosis of CVID was re-evaluated according to the last criteria of the ESID but in dead patients the diagnosis of CVID was according to the criteria of date of diagnosis. Agammaglobulinemia was diagnosed based on low levels of all immunoglobulin isotypes associated with very low numbers of circulating B cells (< 2%), and a normal number of T cells in a symptomatic patient with onset of disease before 5 years. Genetic defects associated with combined immunodeficiency were also excluded in patients with agammaglobulinemia.

The process of this study was reviewed and approved by the Ethics Committee of the Tehran University of Medical Sciences and written informed consent was obtained from patients and/or their parents. All patients received Ig replacement therapy after diagnosis as well as prophylactic antibiotic therapy and individuals with withdrawal and irregular treatment excluded from this study. Clinical information was obtained from medical and chart records review at Children's Medical Center.

2.2. Methods

During the past 20 years, a comprehensive questionnaire was designed and the following data were collected in each case: age at clinical presentation, consanguinity, first presentation, age at diagnosis and age at last follow up, diagnostic delay, history of chronic and recurrent infections, bronchiectasis, autoimmunity, associated allergy, enteropathy, failure to thrive (FTT), tonsils atrophy, lymphoproliferation, and malignancies. In each patient laboratory data were documented, including complete blood count, white blood cell (WBC) differential and lymphocyte subsets percentage (CD3, CD4, CD8 and CD19), and serum levels of IgM, IgG, IgE and IgA. The questionnaire was thoroughly completed for all patients at the time of diagnosis. All patients received regular immunoglobulin replacement therapy (IVIG) with doses of 400–600 mg/kg every 3–4 weeks. Before each time administration of IVIG serum/trough, IgG levels were evaluated and the dose is adjusted so that the trough level just before the next infusion is at least 600 mg/dl. In some cases with bronchiectasis according to the serum trough levels the IVIG increased at a dose of 800 mg/kg. Patients with irregular treatment were excluded from this study. In addition, all patients with refractory to treatment (> 3 breakthrough infections or extremely severe infection on IVIG, bronchiectasis, chronic sinusitis and recurrent acute otitis media) were receiving prophylactic antibiotics such as Azithromycin, cotrimoxazole, amoxicillin and co amoxiclav according to the type of disease. For prophylaxis, antibiotics were used approximately half of a therapeutic dose and one dose per day. To avoid drug resistance, periodically changing antibiotics monthly to every 6 months is practiced. Although the over the counter antibiotics may be used by the patients during the study course. Follow-up visits were documented every month at the time of hospital Ig administration either by interviewing the patients or reviewing patients' hospital records for occasional admissions. Diagnostic delay was defined as the time between onset of symptoms and time of diagnosis. The course of disease was measured as the duration time between diagnosis and the time of either the death or last visit.

2.3. Statistical analyses

Values were presented as frequency (number and percentage), mean ± standard deviation and median (IQR), as appropriate. Fisher's exact test and chi-square tests were used for 2 × 2 comparisons of categorical variables, while t-tests and nonparametric equivalent were used to compare numerical variables. Pearson's and Spearman correlation coefficient were calculated for the assessment of the correlation between parametric and non-parametric variables, respectively. Shapiro-Wilks test used for a check of normality assumption for the variable; so according to the established assumptions, parametric or nonparametric test was done. Kaplan-Meier curve and log-rank test were utilized to compare different survival estimates. Statistical analyses were performed using the SPSS software package, version 22 (SPSS Inc., Chicago, IL, USA).

Table 1
Demographic data of agammaglobulinemia and CVID patients at the time of diagnosis.

Parameters	Total (N = 297)	agammaglobulinemia (N = 102)	CVID (N = 195)	*P value*
Sex ratio (M/F)	203/94	93/9	110/85	< 0.001*
Consanguinity; N (%)#	172(57.9)	47 (46.1)	125 (64.1)	0.004*
Mortality (%)	128 (43.0)	40 (39.2)	88(45.1)	0.610
Age at the study time; median in year (IQR)	14.0 (24.0–7.0)	10.0 (19.0–5.75)	17.0 (28.0–9.0)	0.001*
Age at onset of symptoms; median in year (IQR)	1.0 (5.0–0.75)	1.0 (2.0–0.0)	2.0 (6.0–1.0)	0.001*
Age at the time of diagnosis; median in year (IQR)	7.0 (13.0–2.0)	4.0 (7.0–2.0)	9.5 (16.0–4.0)	0.001*
Delay diagnosis; median in month (IQR)	42.0 (94.0–12.0)	24.0 (60.0–12.0)	52.0 (108.0–13.0)	< 0.001*
Follow-up period; median in year (IQR)	11.5 (19.0–6.0)	9.5 (17.0–4.5)	12.5 (19.0–6.5)	0.024*

CVID; Common variable immune deficiency, M; Male, F; Female.
IQR: range with 75th and 25th percentiles.
* P-value is statistically significant. < 0.05.
# We considered first- and second- cousins marriages as consanguineous relationship in parents with the common ancestor being no more distant than a great grandparent.

3. Results

3.1. Demographics and immunologic parameters

The total number of studied cases that fulfilled inclusion criteria was 297 patients. Of these, 203 patients (56.4% of CVID and 91.2% of agammaglobulinemia) were male and 94 patients (43.6% of CVID and 8.8% of agammaglobulinemia) were female) $P < 0.001$(. Approximately, 58% of evaluated patients) including 125 patients with CVID [64.1%] and 47 patients with agammaglobulinemia [46.1%] (had consanguinity ($P = 0.004$). 128 patients were deceased during the 20-year follow-up rather than 161 patients (99 CVID and 62 agammaglobulinemia) alive patients and 8 patients were unavailable at the last month of the study. Demographics data are shown in Table 1.

The median (IQR) of age at onset of symptom in agammaglobulinemia was earlier than CVID (median IQR 1.0(0.0–2.0) vs. 2.0(1.0–6.0) $P = 0.001$) so agammaglobulinemia patients were diagnosed earlier than CVID. Course of disease in CVID patients was longer than agammaglobulinemia patients [median IQR 12.0 (6.0–19.0) vs. 9.0 (4.0–17.0), $P = 0.024$)]. Although the percentage of $CD4^+$ T lymphocytes was significantly higher in agammaglobulinemia patients, the absolute counts of total lymphocytes from white blood cells were almost equal in the two groups of patients which were in line with a significant reduction of $CD19^+$ B lymphocytes in agammaglobulinemia patients. Immunological parameters, including lymphocyte subsets and serum Ig levels at the time of diagnosis, are shown in Table 2.

3.2. Clinical manifestations and co-morbidities

The most common first presentations in both diseases were infections (particularly sinopulmonary infection) and enteropathies. Enteropathy in CVID was relatively more frequent than agammaglobulinemia; while autoimmunity in agammaglobulinemia was more frequent relatively than CVID as a first presentation. Totally, 16 of 195 CVID patients and 6 of 102 agammaglobulinemia patients presented at the time of onset of chronic sinusitis, 17 CVID patients and 12 agammaglobulinemia patients has firstly manifested pneumonia. Fig. 1 shows the most prevalent first manifestations of agammaglobulinemia and CVID patients.

During the course of the disease, pulmonary infections were the most prevalent clinical manifestations in both groups of patients (133[68.2%] of CVID and 64[62.7%] of agammaglobulinemia, $P = 0.856$, Fig. 2). Other most common clinical complications were enteropathy (116[59.5%] of CVID and 49[48%] of agammaglobulinemia, $P = 0.059$), chronic sinusitis (111[56.9%] of CVID and 48[47.1%] of agammaglobulinemia, $P = 0.106$), and otitis media (97[49.7%] of CVID and 47[46.1%] of agammaglobulinemia, $P = 0.557$), respectively. Bronchiectasis was documented by high-resolution computed tomography scan in 43 of the 195 CVID patients (22.1%) and 15 of the 102 agammaglobulinemia patients (14.7%; $P = 0.129$). Bronchiectasis was not only more common in CVID patients than agammaglobulinemia patient, but also it was recorded in average 10.6 years after the disease onset and usually after diagnosis under Ig replacement therapy. The rate of infectious complications per year is shown in Table 3.

Lymphadenopathy, hepatomegaly and splenomegaly were significantly increased in CVID than agammaglobulinemia patients ($P < 0.001$, $P = 0.002$ and $P < 0.001$, respectively). In this study, 54 of 195 CVID patients (27.7%) and 12 of 102 agammaglobulinemia patients (11.8%) had autoimmunity ($P = 0.002$; Fig. 2). Of note, the main autoimmune complication among agammaglobulinemia patients was rheumatologic diseases (9 out of 12 patients, 75%), but among

Table 2
Immunological data of agammaglobulinemia and CVID patients at the time of diagnosis.

Parameters	Total (N = 297)	agammaglobulinemia (N = 102)	CVID (N = 195)	*P value*
IgG; mg/dl (IQR)	235.0 (469-54.5)	99.0 (298–17.0)	315 (556.7–99.0)	< 0.001*
IgA; mg/dl (IQR)	9.0 (29.0-0.0)	4.0 (19.0–0.0)	10.0 (38.0–2.5)	< 0.001*
IgM; mg/dl (IQR)	22.0 (50.0-5.0)	13.0 (31.5–0.95)	28.0 (60.0–14.0)	< 0.001*
Hemoglobin; g/dL (IQR)	11.8 (12.9-10)	11.3 (12.5–9.72)	11.8 (13.1–10.5)	0.074
WBC (cells/;mm^3)	8500 (11900-6000)	8940 (12575–6942)	8100 (11600–5900)	0.133
Neutrophils; (cells/;mm^3)	3922 (6230-2576)	3078 (7177–1597)	4071 (6027–2907)	0.144
Lymphocytes; (cells/;mm^3)	2627 (4373-1794)	3158 (4975–1563)	2546 (4278–1885)	0.348
$CD3^+$ T cells; (cells/;mm^3)	2096 (3659-1300)	2735 (4432–1241)	1933 (2858–1373)	< 0.049*
$CD4^+$ T cells; (cells/;mm^3)	855 (1581-503)	1150 (2236–541)	802 (1322–459)	< 0.017*
$CD8^+$ T cells; (cells/;mm^3)	1013 (1710-595)	1119 (2240–467)	975 (1481–606)	0.265
$CD19^+$ lymphocytes; (cells/;mm^3)	114 (342-23.4)	14.6 (38.1–2.9)	213 (444–94)	< 0.001*

CVID; Common variable immune deficiency, M; Male, F; Female, WBC: white blood cells.
IQR: range with 75th and 25th percentiles.
* P-value is statistically significant. < 0.05.

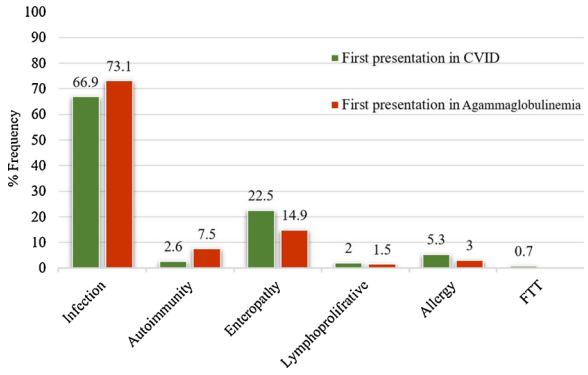

Fig. 1. The first presentation at the time of onset in agammaglobulinemia and CVID patients. FTT: failure to thrive.

CVID patients hematologic and GI autoimmunities were the most common forms (27 and 34 out of 54 patients, respectively). Nine (4.5%) CVID patients (1 with breast cancer, 1 with cystadenoma and diffuse large B cell lymphoma, 6 with Hodgkin's lymphoma, 1 with pulmonary mucosa-associated lymphoid tissue lymphoma) and one (1%) agammaglobulinemia patient (Hodgkin's lymphoma) had a history of malignancy.

3.3. Mortality and cause of death

During the follow-up period, 88 (45.1%) CVID and 40 (39.2%) agammaglobulinemia patients were deceased ($P = 0.2$). By Kaplan-Meier method, there was no statistical difference in cumulative survival rate in any of the groups ($P = 0.694$; the 15 years survival rate in CVID patients was 54.9% whereas in agammaglobulinemia patients was 60.8%; Fig. 3). The median age of death was significantly lower in agammaglobulinemia patients than CVID patients [7.5 (2.2–12.0)] vs. 16.0 (8.0–22.5) years, $P < 0.001$]. The predominant causes of death in CVID patients were infections (meningitis encephalitis, and septicemia in consequence of pneumonia or GI infections), respiratory failure due to chronic lung diseases (CLD) and malignancy; while in agammaglobulinemia patients the infectious causes were slightly more pronounced compared to CLD (Fig. 4). Among 195 CVID patients, 4 patients died from malignancy (3 Hodgkin's lymphomas and 1 breast cancer). Statistical analysis did not show any significant association between the mortality and serum Ig levels and lymphocyte subset counts in any of the groups.

Considering infectious complications, there was a higher rate of otitis media, pneumonia, chronic sinusitis and GI infections in dead patients comparing to alive patients in any of the groups. There was an association between bronchiectasis and mortality in CVID and agammaglobulinemia groups, however, it was not statistically significant ($P = 0.065$ and $P = 0.074$, respectively). Moreover a significant difference was observed between incidence rate of splenomegaly, hepatomegaly and malignancy in deceased CVID patients than alive CVID patients ($P = 0.015$, $P < 0.001$ and $P = 0.027$ respectively) but there was not significant association with in autoimmunity and allergy (Table

Table 3
The rate of infectious complications per year in CVID and agammaglobulinemia patients.

Parameters	CVID Median (IQR)	Agammaglobulinemia Median (IQR)	*P*-value
Otitis media	0.21(0.41-0.09)	0.30 (0.62-0.12)	0.07*
Pneumonia	0.26 (0.56-0.12)	0.37 (0.79-0.12)	0.27
Chronic sinusitis	0.20 (0.40-0.11)	0.20 (0.33-0.11)	0.57
Enteritis	0.25 (0.50-0.07)	0.29 (0.76-0.08)	0.30
Meningitis	0.13 (0.31-0.08)	0.15 (0.21-0.05)	0.58
Oral candidiasis	0.22 (0.82-0.08)	0.23 (0.71-0.15)	0.66

CVID; Common variable immune deficiency.
IQR: range with 75th and 25th percentiles.
* P-value is statistically significant. < 0.05.

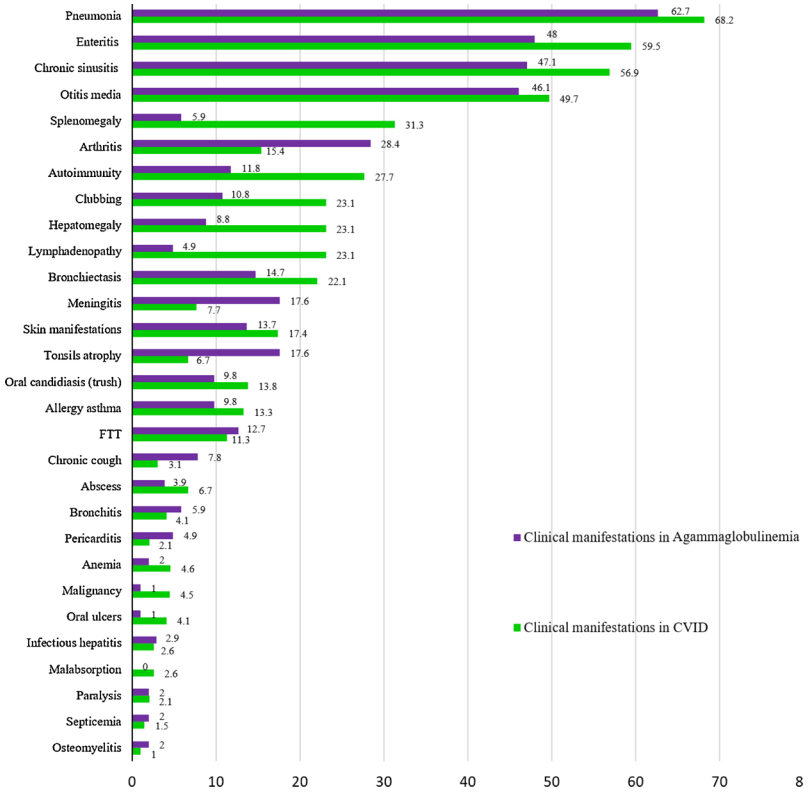

Fig. 2. Comparison of percentage of frequent complications in CVID and agammaglobulinemia patients. FTT: failure to thrive.

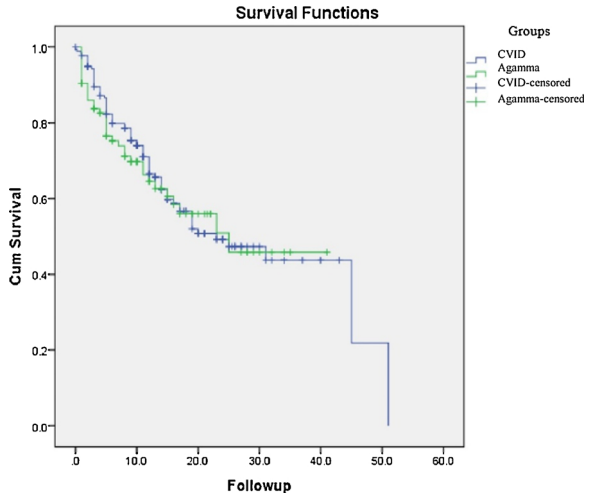

Fig. 3. Kaplan-Meier survival curves for CVID and agammaglobulinemia patients indicating both patients' groups had similar survival.

4, 5**)**. However, neutrophil counts showed a significant decrease in dead CVID patients compared with alive patients ($P = 0.041$). We have also performed a comparison on mean IgG trough level during follow-up time between the dead and alive patients in both CVID and agammaglobulinemia groups. Although the mean levels were lower in deceased patients but the differences were not statistically significant (Figure S1). The mortality rate was also independent from the prescription of prophylactic antibiotics although there is a potential bias of misclassification due to the access of patients to over the counter antibiotics in the country (Figure S2).

Among 62 patients with genetic analysis, 55 patients had X linked agammaglobulinemia and 7 patients had autosomal recessive inheritance. Our agamaglobulinemia patients indicated 48 mutations in *BTK*, 5 mutations in *IGHM*, 2 mutations in *BLNK* and 1 mutation in *CD79A* gene. Six out of 62 patients (9.8%) did not show any variation in the investigated genes and will be enrolled for exome sequencing analysis. Near the half of dead patients (Nineteen patients, 47.5%) had a genetic defect including *BTK* gene variations in 18 patients and *IGHM* variations in 1 case. Eighteen of them were male and one was female in different ages (Early childhood, 3 patients; adolescent, 4 patients and adults, 13 patients).

4. Discussion

We compared here the immunologic profile, demographics parameters, clinical characteristics, and mortality analyses for 297 patients diagnosed and followed-up for more than 2 decades. During the follow-up period, the rate 15-years survival was 54.9% in CVID and 60.8% in agammaglobulinemia, greater than previous studies in our center with 71% in CVID (173 patients mixed with monogenic diseases, 10-years survival) and 78% in agammaglobulinemia (41patients, 5-years survival) [17,25]. Although during the follow-up period, 45.1% CVID and 39.2% agammaglobulinemia patients were deceased, it is related to the cumulative data but mortality rate in 10 years period after 2000 was less than 10% (Fig. 3, Figure S3). We showed that the diagnosis delay in our series was somewhat lower than from our previous studies (17, 25), this rather contradictory result may be due to a longer period of our follow-up in our registry. The time of onset in agammaglobulinemia patients usually begins after the first few months of life, when the maternal IgGs that transferred through the placenta are catabolized and patients are affected by recurrent bacterial respiratory and GI infections in the first two years of life [26]. In different studies, the onset was from one till two years [4,27,28] and in our study, the onset was one year and the median age at the time of diagnosis was 4 years. In addition, the time of onset and the median age at diagnosis in CVID patients were significantly less than previous studies [29,30]. This difference in age at onset and diagnosis with other studies could be due to some reasons, because of the high rate of consanguinity in Iran prevalence of autosomal recessive PADs is high and also there are diverse causative monogenic mutations that can cause earlier onset of patients.

CVID and agammaglobulinemia patients may have heterogeneous patterns of non-infectious complications. Our results were in accordance with recent studies indicating that hepatomegaly, splenomegaly, malignancy, clubbing and autoimmunity were the most common non-infectious findings in CVID and agammaglobulinemia patients [31]. The frequency of autoimmunity in CVID was higher than agammaglobulinemia. In a previous study, we showed that autoimmunity in CVID was higher not only than agammaglobulinemia but also other forms of PADs. The most common autoimmune manifestations were reported to be autoimmune GI diseases, autoimmune hematologic diseases and rheumatologic diseases in CVID and autoimmune rheumatologic disease and autoimmune hematologic diseases in XLA [32]. Arthritis was another of non-infectious complication in both groups, in our previous study we also reported that juvenile idiopathic arthritis (JIA), adult rheumatoid arthritis (RA), juvenile spondyloarthritis (JSpA) and undifferentiated inflammatory arthritis (UIA) are the most frequent rheumatologic disorders in our CVID patients and this also accords with our earlier observations, which showed that the main autoimmune complication among agammaglobulinemia patients was rheumatologic diseases along with hematologic, dermatologic and GI manifestations [33]. Despite of commonly higher autoimmunity prevalence in CVID but as a first presentation, autoimmunity in agammaglobulinemia was more frequent relatively than CVID. Autoimmunity may be one of the first presentations of the PAD even with no considerable history of severe and recurrent infections, so physicians should be alert of autoimmunity to reduce the diagnostic delay. Because the standard treatment does not control autoimmunity in these patients, the early recognition and specific management of these complications

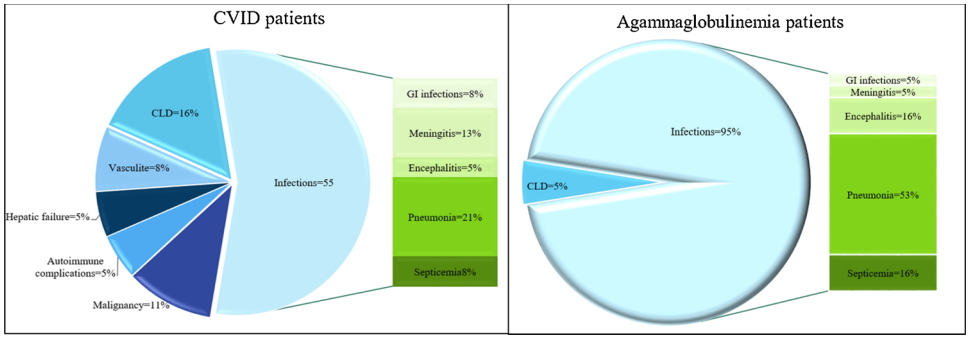

Fig. 4. The predominant causes of death and type of infections in CVID (left) and agammaglobulinemia (right) patients. GI: gastrointestinal. CLD: chronic lung disease.

Table 4
Demographic and immunological data of dead and alive patients in agammaglobulinemia and CVID patients.

Parameters	Agammaglobulinemia (N = 102)		*P value*	CVID (N = 195)		*P value*
	Dead	Alive		Dead	Alive	
Age at the study time; median in year (IQR)	6 (12–3)	13 (22–8)	0.27	11 (19.5–5)	21 (31–13)	< 0.001*
Age at onset of symptoms; median in year (IQR)	1 (2–0)	1 (3–0.5)	0.08	1 (5–0.2)	2 (7–1)	0.37
Age at the time of diagnosis; median in year (IQR)	3.0 (7–2)	5 (7–2)	0.27	8 (14–2)	9 (19–4)	0.33
Delay diagnosis; median in month (IQR)	22 (60–9.7)	34.5 (59–12)	0.298	46.5 (97.2–11.7)	60 (116–12.5)	o.322
Follow-up period; median in year (IQR)	5.(11–1)	13 (20–6.5)	< 0.001*	9 (14–3.7)	15.5 (21–9.5)	< 0.001*
IgG; mg/dl (IQR)	99 (307–0.0)	99.0 (297–23.7)	0.824	330 (552–99)	255 (512–91)	0.781
IgA; mg/dl (IQR)	0.24 (19.0–0.0)	4.5 (19.8–0.0)	0.297	10 (36–2.0)	9.0 (37.7–3.2)	0.708
IgM; mg/dl (IQR)	7 (25.2–0.0)	16 (36–4)	0.074	28.5 (68.2–18)	20 (52–12)	0.321
Hemoglobin; g/dL (IQR)	11.2 (12.3–9)	11.8 (12.5–9.8)	0.332	11.1 (11.9–9.9)	12.4 (13.3–10.6)	0.035*
WBC (cells/;mm^3)	9150 (14220–5775)	8715 (12470–6942)	0.836	7800 (12000–5400)	8500 (11330–6480)	0.405
Neutrophils; (cells/;mm^3)	3060 (6703–1473)	3096 (7463–1768)	0.642	3660 (5661–2406)	4661 (6624–3074)	0.041*
Lymphocytes; (cells/;mm^3)	3692 (6890–2000)	2772 (4392–1373)	0.260	2448 (4252–1710)	2621 (4300–1929)	0.369
$CD3^+$ T cells; (cells/;mm^3)	3329 (4742–1248)	2546 (4121–1189)	0.778	1821 (2762–1225)	2099 (3059–1459)	0.184
$CD4^+$ T cells; (cells/;mm^3)	1115 (2511–316)	1179 (2144–664)	0.466	754 (1282–440)	872 (1480–559)	0.238
$CD8^+$ T cells; (cells/;mm^3)	1721 (2743–1041)	904 (1694–345)	0.017*	961 (1385–485)	1061 (1587–693)	0.217
$CD19^+$ lymphocytes; (cells/;mm^3)	16 (56.8–4.1)	8.3 (36–2.3)	0.331	202 (444–75)	271 (458-102)	0.662

CVID; Common variable immune deficiency, M; Male, F; Female, WBC: white blood cells.
IQR: range with 75th and 25th percentiles.
* P-value is statistically significant. < 0.05.

Table 5
Complications of dead and alive patients at the time of diagnosis in agammaglobulinemia and CVID patients.

Parameters	Agammaglobulinemia (N = 102)		*P value*	CVID (N = 195)		*P value*
	Dead	Alive		Dead	Alive	
Chronic cough (%)	10.0	6.5	0.708	1.1	5.1	0.216
Bronchiectasis (%)	22.5	9.7	0.074	25.0	17.2	0.188
Bronchitis (%)	10.0	3.2	0.207	6.8	2.0	0.257
Clubbing (%)	12.5	9.7	0.748	23.9	21.2	0.559
Allergy asthma (%)	7.5	11.3	0.736	15.9	11.1	0.627
Skin manifestations (%)	17.5	11.3	0.374	14.8	19.2	0.423
Abscess (%)	0.0	6.5	0.153	8.0	4.0	0.256
Oral ulcers (%)	2.5	0.0	0.392	4.5	4.0	1.0
Arthritis (%)	17.5	35.5	0.049*	11.4	19.2	0.140
Failure to thrive (%)	22.5	6.5	0.018*	15.9	8.1	0.097
Tonsils atrophy (%)	17.5	17.7	0.975	6.8	7.1	0.946
Autoimmunity (%)	7.5	14.5	0.357	29.5	25.3	0.511
Splenomegaly (%)	7.5	4.8	0.677	39.8	23.2	0.015*
Hepatomegaly (%)	12.5	6.5	0.309	37.5	11.1	< 0.001*
Lymphadenopathy (%)	5.0	4.8	0.971	28.4	17.2	0.066
Malignancy (%)	0.0	1.6	1.0	8.0	1.0	0.027
Infectious hepatitis (%)	5.0	1.6	0.559	1.0	3.4	0.344
Pericarditis (%)	0.0	8.1	0.066	2.3	2.0	1.0
Anemia (%)	5.0	0.0	0.151	4.5	5.1	1.0
Septicemia (%)	2.5	1.6	1.0	1.1	2.0	1.0
Otitis (%)	50.0	43.5	0.523	51.1	46.5	0.523
Pneumonia (%)	67.5	59.7	0.425	72.7	64.6	0.235
Sinusitis (%)	42.5	50.0	0.459	58.0	53.5	0.544
Meningitis (%)	15.0	19.4	0.573	10.2	6.1	0.295
Enteritis (%)	52.5	45.2	0.469	62.5	55.6	0.335
Osteomyelitis (%)	2.5	1.6	1.0	1.1	1.0	1.0
Oral candidiasis (%)	10.0	9.7	1.0	21.6	7.1	0.004*

CVID; Common variable immune deficiency, M; Male, F; Female, WBC: white blood cells.
* P-value is statistically significant. < 0.05.

should be considered by a clinical immunologists. our results are in consistent with a previous study on CVID subjects that splenomegaly, hepatomegaly and malignancy were associated with worse survival, which represents the direct association of these complications with mortality in CVID patients, so these complications in CVID and agammaglobulinemia patients should be considered by a clinical immunologists [16,34–36].

In addition to the non-infectious complications, infections particularly recurrent respiratory tract infections were the most common complications and first presentation symptoms among both agammaglobulinemia and CVID patients, however, these complications like pneumonia, chronic sinusitis and otitis media were more prevalent in CVID than agammaglobulinemia patients. Recurrent respiratory tract infections often result in long-term sequelae and bronchiectasis. Moreover, our data is in agreement with a previous study that the rate of otitis media, pneumonia, sinusitis and enteritis in deceased patients of both CVID and agammaglobulinemia was more frequent than of survived patients. The current study is in agreement with previous reports signifying low rates of bronchiectasis in agammaglobulinemia patients [3,17,22], but higher rates in CVID [29,37–42]. This difference may be explained by the fact that agammaglobulinemia patients are diagnosed and treated earlier than ones with CVID; another possible

explanation for this phenomenon is the presence of a dysregulated immune response in CVID patients, therefore they are more susceptible to be affected with lung disease even after Ig replacement therapy.

The predominant cause of death in both CVID and agammaglobulinemia patients were infection particularly pneumonia and after that CLD but mortality due to malignancy and autoimmune disorders were seen exclusively in deceased CVID patients. Although the effectiveness of Ig replacement therapy in reducing the incidence of recurrent respiratory tract infections like pneumonia in patients with PAD have been evident [39,43–46], the risk of chronic pulmonary diseases including bronchiectasis and interstitial lung diseases development remain even under this therapy. A possible explanation for this might be that the inability of antibody substitution to reach the mucosal surface for playing a crucial protective role or other factors besides antibody production impairment may contribute to the development of these complications. The causative infections in PADs are mainly encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenza* species [47,48]. Although malignancies usually are less likely identified in agammaglobulinemia patients, they can seriously threat CVID patients [14]. Lymphoma is a most common malignancy in CVID and its mortality rate varied among different cohorts including 8.2% in the US, 3.8% in the UK, 3% in ESID cohort, 2% in a combined Danish-Swedish cohort and 1.8% in an Italian cohort [35,49,50]. In our study, nine cases (4.5%) developed malignant disorders that four cases (4.9%) were deceased including three cases of lymphoma and one breast cancer. These surveys indicated the increased risk of malignancy, especially lymphoma in CVID and this risk increases as the patients survive to an older age [40]. So, earlier diagnosis and precise management of malignancy could help the survival of CVID patients.

We reported previously that comparison between agammaglobulinemia patients showed that age at onset was significantly lower in patients with autosomal forms compared to XLA patients. In addition, variations causing autosomal forms of agammaglobulinemia were confirmed in almost 12% of cases and they account proportionally higher in Iranian cohort; probably due to a higher rate of consanguinity in patients' family [8]. In general, early diagnosis of genetic variations could be helpful for more effective treatment and increased the survival rate of patients. For future studies, the inclusion of patients with other causative genes for agammaglobulinemia could help to elucidate more accurately the effect of different genes on morbidity and mortality of patients can be obtained.

Genetic defects were identified in 88.7% of evaluated patients with agammaglobulinemia and based on the definition of CVID monogenic defects were excluded in these patients. However, in the 11.3% of remaining patients with unsolved agammaglobulinemia and all CVID patients whole genome sequencing should be performed before labeling them as non-monogenic PAD. After this step and within this group of idiopathic PAD patients several differential diagnoses should be examined including digenic or polygenic model of the disease. Moreover the role of environmental factor on epigenetic markers of B cell development should be investigated [11].

This study showed that infections especially respiratory infections were the most common complication and cause of death in both CVID and agammaglobulinemia groups and recent treatment advances even Ig replacement cannot completely control these complications. Routine screening and targeted treatment in patients with risk indicators are important, so we can speculate that increased awareness of general practitioners and pediatricians in order to better diagnosis of PAD patients and the introduction of targeted treatment for the underlying molecular defects can extend the life expectancy in these patients.

Conflict interest

None

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.imlet.2019.05.001.

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