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# Allergic-like Disorders and Asthma in Patients with Common Variable Immunodeficiency: a Multi-Center Experience

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## Abstract

**Objective:** Common variable immune deficiency (CVID) encompasses a variety of diseases characterized by disturbed immunoglobulin (Ig) production and various immune dysregulations. Scarce data are available regarding relationships between CVID and allergic diseases. Here we examined possible associations between allergies and CVID.

**Methods:** For this multicenter study, we prospectively enrolled 79 adult CVID patients (≥18 years) who were diagnosed and treated between 2002–2017 at the Hadassah-Hebrew University and Shaare Zedek Medical Centers, Jerusalem, Israel. These patients were examined for allergic manifestations. Patient evaluation comprised medical history, physical examination, skin allergen testing, complete blood count, serum immunoglobulins, IgE levels, and pulmonary function tests.

**Results:** After implementing exclusion criteria, 29 patients were included in the final analysis. Allergic-like disorders were diagnosed in 65% of CVID patients with non-elevated serum IgE levels. Moreover, allergic CVID patients exhibited a higher prevalence of bronchiectasis on chest CT. Autoimmunity was diagnosed in 41.3% of CVID subjects. The type I allergy detected in our study was non-IgE mediated.

**Conclusions:** Timely diagnosis and stratification of allergy in CVID patients is expected to improve their outcome and quality of life, as well as promote appropriate treatment and better management of pulmonary exacerbations.

**Keywords:** common variable immune deficiency; allergic disorders; asthma; incidence rate; clinical characteristics; diagnosis.

## Abbreviations

AD, Atopic dermatitis

AID, Autoimmune diseases

AR, Allergic rhinitis

CD, Cluster of differentiation

CT, Computed tomography

CTLA-4, Cytotoxic T-lymphocyte-associated protein 4

CVID, Common variable immune deficiency

ESID, European society of immunodeficiencies

FEV1, Forced expiratory volume in one second

FVC, Forced vital capacity

Ig, Immunoglobulin

IPEX, Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome.

IVIG, Intravenous immunoglobulin treatment

LABA, Long-acting  $\beta$ 2-agonist;

LRBA, Lipopolysaccharide-responsive beige-like anchor protein

PID, Primary immune deficiencies

RAST, Radioallergosorbent test

SLE, systemic lupus erythematosus

SPT, Skin prick test

Th, T helper

Tregs, Regulatory T cells

## Introduction

Common variable immune deficiency (CVID) is characterized by hypogammaglobinemia, decreased specific immunoglobulin (Ig) G titers, recurrent sinopulmonary infections, and an exclusion-based diagnosis (1, 2). Patients with CVID commonly exhibit immune dysregulation and the emergence of organ-specific and systemic autoimmune diseases (AID)(3). including pernicious anemia, psoriasis, and systemic lupus erythematosus (SLE)(4). Widespread use of intravenous immunoglobulin (IVIG) replacement therapy has reduced infections among CVID patients, such that non-infectious complications (e.g., AID, chronic intestinal inflammation, and lung disease) now constitute the major cause of morbidity and mortality in this patient population (2, 5).

The pathogenic mechanisms underlying the development of non-infectious complications in CVID patients remain undetermined, although various laboratory findings provide some clues. For example, CVID patients with AID exhibit increased signature genes of interferon, which results in the expansion of innate lymphoid cells that are associated with protective and pathogenic immune responses. A similar gene expression profile has been reported in SLE and other chronic inflammatory diseases (2).

The prevalence of asthma in CVID patients varies among studies, ranging from 6.5% to 25%(6-8). A study from Minnesota reported a history of asthma in 31% of patients with CVID or selective IgA deficiency,

compared to in 12% of healthy controls (6). Mechanisms for the potential association between CVID and asthma are unknown, although mutations in the *TNFRSF13B* gene that have been found in CVID patients are linked to increased risk of asthma development (9). Few studies have examined associations between CVID and other allergic diseases, such as allergic rhinitis (AR) and atopic dermatitis (AD) (10). Interestingly, laboratory evaluation of CVID patients has revealed that IgE levels are not elevated despite presentation of allergic-like reactions. Hence, further studies are needed to elucidate the underlying immunological mechanism in these patients (11).

In the present study, we aimed to define the incidence rates and clinical and laboratory features of various allergic disorders among adult CVID patients. We hypothesized that allergic disorders were prevalent among CVID patients, and were under-diagnosed and untreated.

## Materials and methods

### Study population

Our study included adult patients (age  $\geq 18$  years) who were diagnosed with CVID between January 2002 and April 2017, and who were treated at the Hadassah-Hebrew University and Shaare Zedek Medical Centers, Jerusalem, Israel.

### Study design

For this prospective multi-center study, we first compiled a list of CVID patients obtained from both medical centers. From the patients' computerized medical records, we retrieved data regarding clinical and laboratory features, treatment, and outcome. Following data collection, a telephone survey was conducted. All patients with clinical symptoms of atopy were asked to visit the clinical immunology clinic for complete history, physical examination, aeroallergen skin testing, and pulmonary function tests.

### Skin prick testing for aeroallergens

Skin prick tests (SPT) were conducted using the following aeroallergens: Bermuda grass pollens, *Artemisia*, olive, molds mixture, mites mixture (*Dermatophagoides farinae* and *pteronyssinus* 1:1), grasses mixture (seven standardized grass pollens), Arizona cypress, *Aspergillus fumigatus*, feathers, *Parietaria*, weeds mixture (four equal parts of cocklebur, rough pigweed, English plantain, and lamb's quarters), dog hair and dander, and cat. The allergen extracts used in this study were manufactured by ALK, Denmark. As negative and positive controls, we used normal saline solution (0.9% sodium chloride) and histamine (1 mg/mL), respectively. A wheal size of  $\geq 3$  mm greater than the negative control was considered positive.

### Inclusion criteria

All patients included in this study met three criteria. First, all patients met the European Society for Immunodeficiencies (ESID) updated diagnostic criteria for CVID (12). Second, patients displayed classical clinical manifestations of an allergic disorder. This included clinical expression of an atopic disorder, such as urticaria with or without angioedema, AD, anaphylactic reaction, AR, allergic/vernal conjunctivitis, and asthma (7). Third, patients showed results of spirometry, with or without methacholine challenge, that were compatible with asthma, including a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) of  $<70\%$  and an increase of over 12% in FEV1 or of 15–25% in forced expiratory flow following treatment with bronchodilators (13).

### Ethical considerations

The study was approved by the institutional review boards of the Hadassah-Hebrew University and Shaare Zedek medical centers (numbers 0077-18-HMO and 0197-18-SZMC, respectively). The patients gave their oral informed consent prior to the telephonic survey. Subsequently, patients who visited the immunology clinic signed an informed consent form.

## ***Statistical analysis***

Statistical analysis was performed using SPSS and Minitab statistical software, version 21 (IBM SPSS, Inc. Chicago, Illinois, USA). To assess the strength of the linear association between two quantitative variables, we calculated the Pearson correlation coefficient. We analyzed the association between two qualitative parameters using the Chi-square and Fisher's exact test. A *t*-test or non-parametric Mann-Whitney test was applied to analyze associations between quantitative and qualitative variables within the two categories. To evaluate the association between a quantitative variable and a categorical variable within three categories or more, we applied either the ANOVA model or the Kruskal-Wallis non-parametric test. All applied tests were two-tailed, and a *p* value of  $\leq 0.05$  was considered to indicate statistical significance.

## **Results**

### ***Study cohort***

Based on the required parameters, computerized analysis generated a list of 79 patients. We reviewed the computerized medical data for all of 79 patients, and 35 patients were excluded from the study due to death, loss to follow-up, or failure to meet the inclusion criteria for CVID diagnosis. The remaining 47 patients were contacted for telephone surveys. Following the telephone surveys, seven patients were excluded due to loss to follow-up, three patients failed to meet the research inclusion criteria, and seven patients declined to participate (Figure 1). Thus, the final analysis included 29 patients.

The mean ages at the onset of CVID symptoms and diagnosis were 24 years ( $\pm 17.9$  years) and 39 years ( $\pm 13.4$  years), respectively. The mean age at the initiation of IVIG treatment was similar to the mean age at diagnosis. Analysis of the collected data revealed that 19 patients suffered from allergic-like symptoms, while 10 patients had no such symptoms.

We examined each study participants' records along with the data obtained from study examinations. Clinical parameters were similar between the groups with and without allergic-like symptoms (Table 1). The Mann-Whitney U-test revealed no statistically significant differences ( $p < 0.05$ ) between the groups with and without allergic-like symptoms in terms of the patient age distribution, ethnic diversity, sex distribution, and number of hospitalizations. However, the groups showed statistically significant differences in clinical presentation at the time of diagnosis. A chi-square test of independence revealed no significant association between gender (male/female) and allergic status ( $p = 0.2$ ). However, we did find that the presence of bronchiectasis on chest CT was significantly associated with allergic-like symptoms ( $p = 0.013$ ).

Table 2 presents the quantitative parameters of the population study. We evaluated possible correlations between the different quantitative parameters using different statistical analyses. A moderate positive correlation (Figure 2B) was found between age at onset of symptoms and age of diagnosis ( $p = 0.01$ ). We also found a strong positive correlation (Figure 2A) between age at CVID diagnosis and age when starting treatment ( $p < 0.00001$ ). No statistically significant association (Figure 2C) was found between age at CVID diagnosis and IgG levels at diagnosis ( $p = 0.2$ ).

### ***CVID and allergic-like disorders***

Table 3 presents the quantitative parameters of the group of patients with allergic-like symptoms. The majority of CVID patients in this study (65%) expressed or were diagnosed with allergic-like symptoms, and 68.4% of these patients had more than one allergic manifestation. Symptoms included the following: asthma (42.1%; 8/19), allergic conjunctivitis (47%; 9/19), AR (79%; 15/19), and AD (5.3%; 1/19) (Figure 3).

Among the patients suffering from allergic-like symptoms, 57.9% (11/19) managed to undergo SPT, all of whom had negative results. Seasonal allergic symptoms were identified in 42.1% of patients (8/19), and 68.4% of patients (13/19) were using prescribed controller medications, including systemic or inhaled corticosteroids (ICS) and anti-histamines. However, despite the known IgE-mediated pathogenesis of these allergic disorders, the patients did not exhibit elevated IgE levels (mean,  $4.35 \pm 5.8$  mg/dL).

### ***CVID and autoimmunity***

The correlation between autoimmunity and CVID is well established (3, 12, 13). Accordingly, a medical background of autoimmunity was diagnosed in 41.3% (12/29) of our present study population. AID included celiac (N = 2), immune thrombocytopenia purpura (N = 2), Hashimoto's thyroiditis (N = 2), and other diseases. Supplementary Figure 1 presents a detailed distribution of autoimmunity. The group of patients with AID exhibited a mild female predominance, with a female-to-male ratio of 7:5.

## **Discussion**

Although CVID manifestations are well described, little is known about the possible relationship between CVID and allergy (8, 11). Moreover, the presence of immediate-type allergic reaction without elevated serum IgE, as seen in our present cohort, is not fully understood (14). In this study, we analyzed CVID patients' medical records and then performed phone surveys and outpatient clinical examinations, which enabled us to gather a wide array of demographic and medical information about these patients.

We identified allergic-like disorders in 65% of the patients—most commonly AR (79%) and conjunctivitis (47%), followed by asthma (42.1%). This incidence was higher than in the general population, supporting our research hypothesis. A similar retrospective investigation reviewed the electronic medical records of 160 patients from the USA, and reported asthma and AR prevalence rates of 37.5% and 63%, respectively—similar to in our study. Interestingly, that report also showed that only 11% of patients with AR were detected with a specific IgE, and only 10% of patients with asthma were found to have an allergic trigger (15). In another study, allergy was confirmed by specific IgE presence in only 5.6% of Brazilian patients with CVID (11).

In our present study, all patients who underwent SPT showed negative results and had non-elevated IgE levels. However, 42.1% of the patients mentioned suffering from seasonal allergic symptoms, and 68.4% were using prescribed controller medications. There remains a need for further laboratory investigations of allergic diseases in CVID patients, such as basophil activation testing and flow cytometry. The findings of such studies could enable prompt diagnosis and treatment, which may lead to improved outcome, decreased morbidity, and increased quality of life.

A review of the literature revealed that CVID patients who test negative for specific IgE antibodies and are suspected of having allergic asthma, have also presented positive responses to bronchial provocation tests with allergens (8). In our present cohort, the analyzed clinical parameters did not differ between patients with and without allergic-like symptoms. However, patients with allergic-like symptoms showed a higher prevalence of bronchiectasis on chest CT. Approximately 30–60% of CVID patients develop chronic lung disease, most commonly bronchiectasis, despite IVIG treatment and antibiotic prophylaxis. Previous studies have reported that bronchiectasis development in CVID patients is correlated with the following parameters: higher inflammatory response, lower CD4<sup>+</sup> T cells count (< 700 cells/ $\mu$ L), low IgM levels, older age, and history of pneumonia (16). These immunological changes were not explored in our present investigation, and

further studies are warranted. Understanding the pathogenesis of allergic-like disorders will enable personally tailored treatment.

AID are reported in an estimated 33.2% of CVID patients, with no significant gender differences (12). Similarly, in our present patient population, 41.3% had a medical background of autoimmunity. In the group of patients with AID, the female-to-male ratio was 7:5, showing a slight female predominance.

It is important to note that allergies and autoimmunity can both result from immune dysregulation. DNA sequencing has revealed genetic variation in the *FOXP3* gene among children simultaneously suffering from allergic and autoimmune diseases (17). Accordingly, *FOXP3* mutations reportedly lead to decreased Tregs or functional defects, such as in patients with immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX), phenotypically expressed with autoimmune endocrinopathy, immune-mediated cytopenias, and allergic dysregulation, including food allergy and eczematous dermatitis (18). Atopy is also observed in other primary immune dysregulation disorders involving Tregs dysfunction, such as cytotoxic T-lymphocyte-associated protein (CTLA)-4 haploinsufficiency and LPS-responsive beige-like anchor protein (LRBA) deficiency (19).

The mechanisms underlying allergic diseases are mainly mediated through signaling of the interleukin-4 (IL-4) and IL-13 pathways, and their common IL-4 receptor  $\alpha$  chain (IL-4R $\alpha$ ). These pathways regulate Th2-mediated response, IgE synthesis, and allergic tissue responses, such as airway inflammation, mucus secretion, and possibly bronchiectasis development in asthma. For example, in vivo inactivation of IL-4R $\alpha$  leads to increased transcription of IL-4 and IL-13, thus resulting in elevated IgE levels, goblet cell metaplasia of the bronchial epithelium, and influx of eosinophils into the airway, which promotes airway inflammation and hyper-reactivity (20).

Greater understanding of the cytokine pathways in allergic disorders has led to the development of targeted biological treatments. Dupilumab, a human monoclonal antibody targeting the IL-4R $\alpha$ , has been used in patients with persistent moderate-to-severe asthma with or without eosinophilia, and is reportedly effective in terms of reducing asthma exacerbations after withdrawal of long-acting  $\beta$  agonists (LABA) and ICS, improved lung function and decreasing T helper cell (Th2) inflammatory markers (21). Dupilumab efficacy has also been described in patients with asthma and perennial AR, yielding significant improvement of nasal symptoms when added to ICS and LABA therapy (22). Moreover, recent studies suggest the efficacy of dupilumab in primary immune deficiencies, such as hyper IgE syndrome due to STAT3 loss-of-function (23, 24). Thus, it is plausible that dupilumab treatment could have benefits in CVID patients, with regards to asthma symptoms and Th1-shift-mediated attenuation of recurrent infections and bronchiectasis.

Our present study has several limitations. Despite the multicenter enrollment of patients, the final sample size was small, in accordance with the observational nature of the study and the low prevalence of CVID in the general population. Therefore, our conclusions are derived from a hypothesis-generated study, and serve only as a proof of concept. Larger confirmatory studies are needed to strengthen our conclusions. Additionally, with regards to the diagnosis of allergic disorders, no laboratory evidence of atopy was demonstrated in this study, and pulmonary function test and SPT were performed in only some cases. Allergic disorders were diagnosed based on typical clinical manifestations, seasonal appearance of complaints, occurrence of symptoms during childhood or before CVID diagnosis, patient-reported specific irritants, and appropriate response to on-demand therapy with ICS and anti-histamine therapy. The patients exhibited classic clinical symptoms associated with allergic disorders, in parallel with negative SPT results and low IgE, leading us to assume that atopy was mediated through a non-IgE mechanism. However, our study did not include molecular immuno-phenotyping. Therefore, we have defined the atopic symptoms in our cohort as “allergic-like” disorders.

## Conclusions

Our present study revealed that allergic-like disorders were prevalent in a cohort of CVID patients, who were under-diagnosed and untreated for allergic diseases. These findings emphasize the need for early diagnosis and appropriate care of allergic disorders among CVID patients. The immune mechanism underlying allergic-like disorders in our patient cohort is thought to be non-IgE mediated, and could plausibly be a T-cell-associated mechanism, similar to in other Tregs disorders. Treatment with dupilumab therapy could potentially reduce airway inflammation, hyper-reactivity, and bronchiectasis in these patients. The present findings warrant further investigation and clinical trials.

## **Declaration of interest**

All authors have no conflict of interest.

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## **Data Availability**

The data used to support the finding of this study are included within the article and supplemental material

## **Authorship contribution**

LR\*- data collection, physical examination of patients and writing of manuscript; OS\* – study design, immune consultation and manuscript revisions, OT, EK- data collection; YR, AT- immune consultation and manuscript review, AYH- immune consultation, YT - Principle investigator, research initiator and study supervision. \* Equally contributed and should be considered as first authors.

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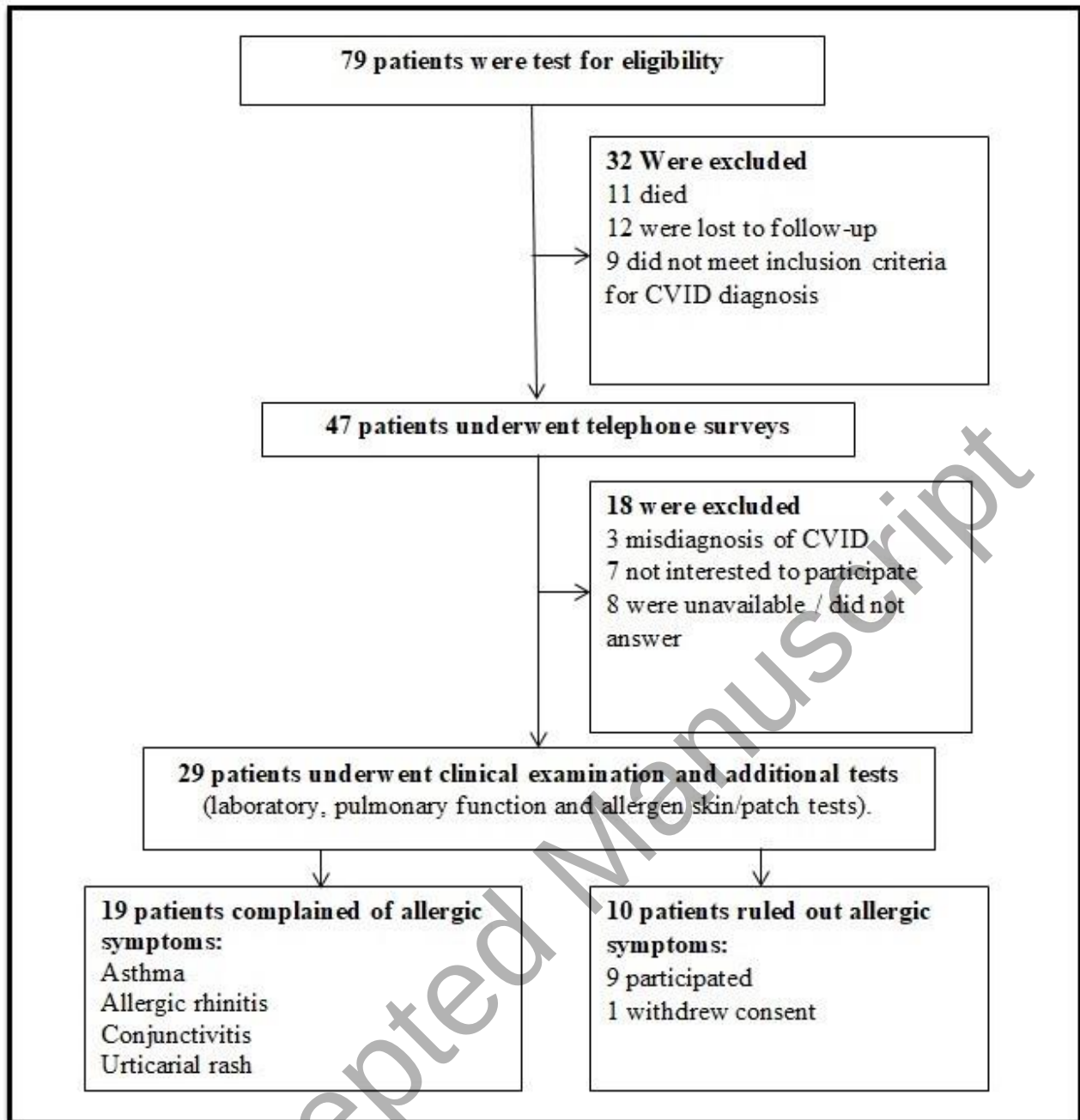


**Figure 1-** Study population, screening, exclusion and follow up

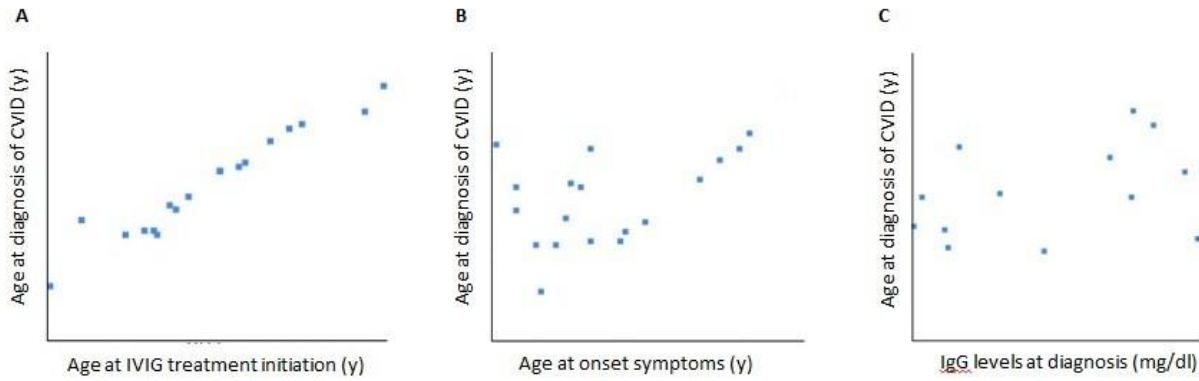


**Figure 2** - Correlations found between quantitative parameters; (A) Strong positive correlation between age at diagnosis of common variable immunodeficiency (CVID) and age when starting intravenous immunoglobulin (IVIG) treatment (Pearson correlation coefficient 0.96, p value <0.00001). (B) Moderate positive correlation between age at diagnosis of CVID and age of symptoms onset (Pearson correlation coefficient 0.5, p value 0.01). (C) No statistically significant correlation between age at diagnosis of CVID and age when starting IVIG treatment (Pearson correlation coefficient 0.37, p value 0.2).

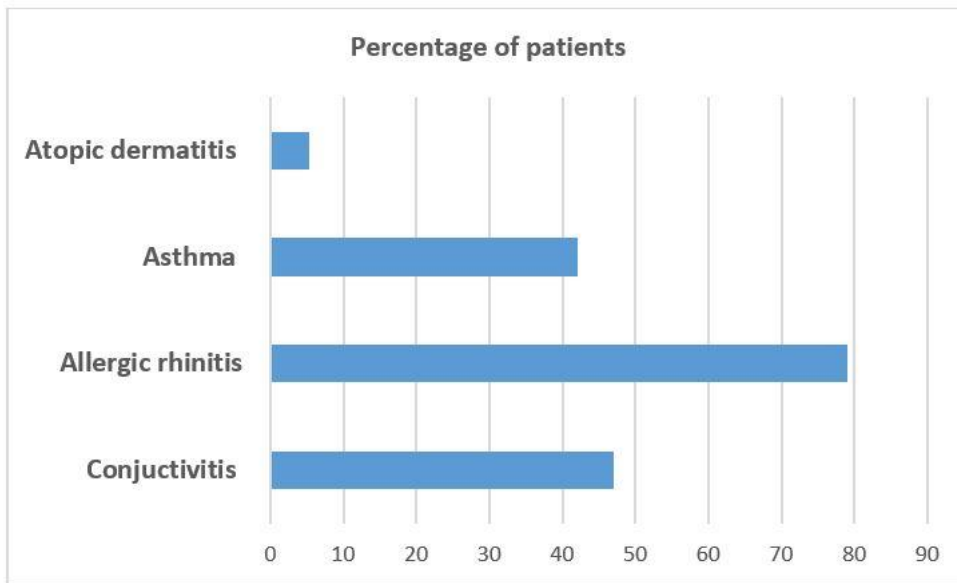


**Figure 3** – Allergic-like disorders distribution among CVID patients.

**Table 1:** General characteristics of the study participants.

| <b>Characteristics</b>                            | <b>Allergic-like group</b> | <b>Non- allergic group</b> |
|---------------------------------------------------|----------------------------|----------------------------|
| <b>Mean Age years (range: min-max)</b>            | 48.7 (29-76)               | 50 (29-82)                 |
| <b>Female sex- no. ( %)</b>                       | 12 (63.1%)                 | 4 (40%)                    |
| <b>Ethnicity – no. /total no. (%)</b>             |                            |                            |
| <b>Jewish</b>                                     | 17/19 (89.4%)              | 8/10 (80%)                 |
| <b>Arab</b>                                       | 2/19 (10.6%)               | 2/10 (20%)                 |
| <b>Medical history – no. /total no. (%)</b>       |                            |                            |
| <b>T2DM</b>                                       | 2/19 (10.5%)               | 0/10 (0%)                  |
| <b>IHD</b>                                        | 1/19 (5.2%)                | 0/10 (0%)                  |
| <b>HTN</b>                                        | 2/19 (10.5%)               | 0/10 (0%)                  |
| <b>CHF</b>                                        | 1/19 (5.2%)                | 0/10 (0%)                  |
| <b>Others*</b>                                    | 3/19 (15.7%)               | 1/10 (1%)                  |
| <b>CVID in family members- no. (%)</b>            | 3 (15.7%)                  | 0 (0%)                     |
| <b>Presentation at diagnosis- no. (%)</b>         |                            |                            |
| <b>Recurrent sinusitis</b>                        | 11/19 (57.9%)              | 1/10 (1%)                  |
| <b>Recurrent pneumonia</b>                        | 15/19 (78.9%)              | 3/10 (30%)                 |
| <b>Recurrent Otitis Media</b>                     | 2/19 (10.5%)               | 0/10 (0%)                  |
| <b>Diarrhea/ enteropathy</b>                      | 5/19 (26.3%)               | 0/10 (0%)                  |
| <b>Others (viral infection/UTI/rash)</b>          | 3/19 (15.7%)               | 1/10 (1%)                  |
| <b>Hospitalized <math>\geq 1</math> – no. (%)</b> | 14 (73.6%)                 | 3 (30%)                    |
| <b>Bronchiectasis in chest CT</b>                 | 10/13 (76.9%)              | 1/6 (16.6%)                |

**no.** –number, **T2DM** – Type 2 Diabetes mellitus, **IHD**- ischemic heart disease, **HTN**- hypertension, **CHF**- congestive heart failure, **CVID**- common variable immunodeficiency; **CT**-computerized tomography; **UTI**- urinary tract infection.

\*others include medical background of autoimmunity, which is discussed separately, malignancies, short stature, elevated liver function tests and G6PD.

**Table 2:** Quantitative characteristics of the general study population.

| <b>Quantitative Characteristics:</b>                                                       | <b>Number of patients records</b> | <b>* Mean<br/>(Standard Deviation)<br/>** Median<br/>(range: minimum-maximum)</b> |
|--------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------|
| Age at onset of CVID symptoms (years)                                                      | 19                                | *24.63 (17.9)<br>** 20 (1-62)                                                     |
| Age at time of diagnosis of CVID (years)                                                   | 20                                | *38.97 (13.39)<br>** 40 (13-64)                                                   |
| Age at onset of IVIG treatment (years)                                                     | 18                                | *38.4 (14.28)<br>*37.5 (13-66)                                                    |
| IgG levels at diagnosis (mg/dl)<br>Normal average levels 994 mg/dl, (range 639-1349 mg/dl) | 15                                | *260.4 (184.1)<br>**250 (26-514)                                                  |
| IgA levels at diagnosis (mg/dl)<br>Normal average levels 171 mg/dl, (range 70-312 mg/dl)   | 14                                | *24.25 (20.9)<br>**24 (0-59)                                                      |
| IgM levels at diagnosis (mg/dl)<br>Normal average levels 156 mg/dl, (range 56-352 mg/dl)   | 16                                | *40.25 (67.8)<br>**17 (0-248)                                                     |

**Table 3:** Quantitative characteristics of the allergic-like patients group.

| Quantitative Characteristics:                                                       | Number of patients records | * Mean<br>(Standard Deviation)<br>** Median<br>(range: minimum-maximum) |
|-------------------------------------------------------------------------------------|----------------------------|-------------------------------------------------------------------------|
| Age at onset of allergic symptoms (y)                                               | 16                         | *22.81(17.2)<br>**22.5 (3-52)                                           |
| IgE levels ( mg/dl)<br>Normal average levels 13.2 mg/dl, (range 1.53-114 mg/dl).    | 9                          | *4.35 (5.8)<br>**1 ( 1-17.2)                                            |
| <i>FEV</i> <sub>1</sub> (percent predicted)<br>Normal range > 80%                   | 8                          | *84.1 (14.11)<br>**85 (63-105)                                          |
| <i>IgG</i> <sub>1</sub> levels ( mg/dl)<br>Normal levels 60-70% of total IgG levels | 7                          | *458.71 (678.3)<br>**167 (30-1953)                                      |
| <i>IgG</i> <sub>2</sub> levels ( mg/dl)<br>Normal levels 20-30% of total IgG levels | 7                          | *413.58 (830.4)<br>**91 (9-2280)                                        |
| <i>IgG</i> <sub>3</sub> levels ( mg/dl)<br>Normal levels 5-8% of total IgG levels   | 7                          | *38.39 (69.86)<br>** 14.5 (1.3-195)                                     |
| <i>IgG</i> <sub>4</sub> levels ( mg/dl)<br>Normal levels 1-4% of total IgG levels   | 7                          | *7.43 (14.46)<br>** 1.9 (0-40)                                          |