



Risk Factors of Bronchiectasis in Adult Patients with Common Variable Immunodeficiency

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ABSTRACT

Objective: Common Variable Immunodeficiency (CVID) is a heterogeneous immune disorder characterized by frequent and recurrent upper and lower respiratory tract infections. Although immunoglobulin (Ig) replacement therapy (IgRT) reduces the frequency of infections, complications due to infections of the respiratory tract, particularly bronchiectasis, is still challenging and occur in approximately 20% of patients. Therefore, we aimed to identify independent predictors of bronchiectasis in adult patients with CVID.

Materials and Methods: We retrospectively analyzed the hospital records of 45 CVID patients (26 male, 19 female). Additionally, we classified the patients according to the presence of bronchiectasis. Bronchiectasis was confirmed by high resolution computed tomography of thorax.

Results: Forty-five patients with CVID (F:19 [42.2%], M: 26 [57.8%]) were included in the study (age: 36.52 ± 12.86). Bronchiectasis was observed in 60% of the study group. Univariate regression analysis revealed that IgG levels (OR: 4.889, 95% CI, 0.485-0.959, p: 0.012) and IgA levels (OR: 2.559, 95% CI, 0.097-1.235, p: 0.030) at the time of diagnosis and the percentage of switched memory B cells (OR: 0.848, 95% CI, 0.730-0.984, p: 0.030) were significantly associated with bronchiectasis. Multivariate regression analysis showed that a lower percentage of switched memory B cells (OR: 0.853, 95% CI, 0.733-0.991, p: 0.038) and a low platelet count (OR: 1.000, 95% CI, 1.000-1000, p: 0.026) were also independent predictors of bronchiectasis.

Conclusion: Clinicians should be alert for CVID patients with reduced switched memory B cells and low platelet counts in order to detect and treat complications associated with bronchiectasis at an early stage.

Keywords: Switched memory B cells, bronchiectasis, platelets, Common Variable Immunodeficiency

INTRODUCTION

Common Variable Immunodeficiency (CVID) is a heterogeneous immune disorder characterized by frequent and recurrent upper and lower respiratory tract infections, autoimmune disorders, granulomatous diseases and predisposition to malignancy (1, 2). In addition, CVID is the most common symptomatic antibody disorder in adults (1). In the absence of other well-defined immunodeficiency conditions, CVID is diagnosed with low levels of immunoglobulin (Ig) G (IgG), IgA and/or IgM, and inadequate antibody response to vaccines or infections (3, 4). Ig replacement therapy (IgRT) either by the intravenous or subcutaneous route is the cornerstone of treatment. Although IgRT, use of prophylactic antibiotics

and monoclonal antibodies such as infliximab, rituximab, adalimumab etc. reduce the frequency of infections, complications due to recurrent and frequent infections of the respiratory tract, particularly bronchiectasis and granulomatous lung disease, are still challenging and occur in approximately 20% of patients (5). In this study, we aimed to investigate the risk factors associated with bronchiectasis in adult patients with CVID who were followed-up at our Clinical Immunology Department.

MATERIALS and METHODS

In our study, we retrospectively analyzed the data in the personal hospital records of 45 patients (26 male, 19 female), in case they have been sufficient. CVID was

diagnosed according to the updated diagnostic criteria of the European Society for Immunodeficiency (ESID) (3). Bronchiectasis have been confirmed by high-resolution computed tomography. The study protocol was approved by the Ethics committee. Informed consent was obtained from study participants.

Serum Ig concentrations (IgG, IgM, IgA, and IgE) were determined by particle-enhanced immunonephelometry using a Siemens BN II/BN ProSpec system (Eschborn, Germany). Peripheral blood lymphocyte subsets were measured with a BD FACSCanto II 8-color flow cytometer system (Erembodegem, Belgium) with fluorescent labeled antibodies. CD3⁺ T cells, helper T cells (CD4⁺ T cells), cytotoxic T cells (CD8⁺ T cells), CD19⁺ B cells, natural killer (CD3⁻ CD16⁺ CD56⁺) cells, switched memory (IgD⁻ IgM⁻ CD27⁺) B cells, and recent thymic emigrant (CD4⁺ CD31⁺ CD45RA⁺) T cells were measured.

Spirometric measurements were obtained with an nSpire ZAN 100 spirometer. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), peak expiratory flow (PEF), mean expiratory flow 25-75% and FEV1/FVC were recorded. FEV1 \geq 80% of the predicted ratio was considered normal.

A statistical analysis was performed with IBM SPSS Statistics, Version 22 software (New York, United States). Parametric statistics were presented as mean \pm standard deviation and nonparametric statistics were expressed as median (minimum–maximum). Descriptive data were presented as frequencies and percentages and compared using the Chi-square test. Comparisons between baseline characteristics were performed with an independent Student's t-test or Chi-square test where appropriate. A binary logistic regression analysis was performed to determine the independent predictors of bronchiectasis.

RESULTS

Forty-five patients with CVID (F: 19 [42.2%], M: 26 [57.8%]) were included in the study (age: 36.52 \pm 12.86). There was parental consanguinity in 53.3% of the patients (parents were from the same village in 68.9% of patients) There was bronchiectasis in 60% of the patients. The mean diagnostic delay was 104.22 \pm 91.9 months. Including the 13 (28.9%) receiving subcutaneous IgRT, all patients have been receiving IgRT. Baseline demographic, clinical, and laboratory parameters of the patients are summarized in Table I.

In the current study, patients with bronchiectasis had lower IgM levels, CD4/CD8 ratios and percentages of B cells at the time of diagnosis. Additionally, patients with bronchiectasis had lower FEV1, PEF, MEF25-75 and FEV1/FVC, but this difference was not statistically significant.

Univariate regression analysis revealed that IgG levels (OR: 4.889, 95% CI 0.485-0.959, p: 0.012), IgA levels (OR: 2.559, 95% CI, 0.097-1.235, p: 0.030) at the time of diagnosis and the percentage of switched memory B cells (OR: 0.848, 95 % CI, 0.730-0.984, p: 0.030) were significantly associated with bronchiectasis. Multivariate regression analysis showed that a lower percentage of switched memory B cells (OR: 0.853, 95 % CI, 0.733-0.991, p: 0.038) and a low platelet count (OR: 1.000, 95 % CI, 1.000-1000, p: 0.026) were also independent predictors of bronchiectasis (Table II).

DISCUSSION

CVID is the most common symptomatic immune disorder in adults with a deficiency of switched memory B cells (5, 6). Although adequate Ig replacement in addition to use of prophylactic antibiotics and monoclonal antibodies such as infliximab, rituximab, adalimumab etc. have reduced the mortality and morbidity rates associated with CVID, complications due to recurrent and frequent infections of the respiratory tract, particularly bronchiectasis and granulomatous lung disease, are still challenging and occur in approximately 20% of patients (5).

In our study group, parental consanguinity was found in 53.3% of patients, which was an unexpectedly high rate. In studies conducted in Turkey, Ardeniz et al. reported a rate of 30% and Musabak et al. reported a rate of 12.9% for consanguineous marriages (7, 8). In studies conducted in other countries, Oksenhendler et al. and Aghamohammadi et al. reported lower rates at 5.4% and 8% , respectively (9, 10). Additionally, in this study, 45 Turkish CVID patients were classified according to the presence of bronchiectasis. Bronchiectasis was reported in 60% of these CVID patients. Thickett et al. reported that 51% of patients with CVID had bronchiectasis (11). In another study consisting of 27 CVID and 10 XLA patients, 55% of the patients had bronchiectasis (12). As far as we know, the highest percentage for bronchiectasis was given as 73% in a study by Kainulainen et al (13). In Turkey, Ardeniz et al. reported that 48% of patients with CVID had bronchiectasis (7).

Table I: Baseline demographic, clinical, and laboratory parameters of the study population

	Total (n=45)	Bronchiectasis (-) (n=18)	Bronchiectasis (+) (n=27)	<i>p</i>
Gender (female), n(%)	19 (42)	9 (50)	10 (37)	0.388
Age	36.52 ± 12.86	36.94 ± 15.62	35.52 ± 10.96	0.915
Consanguinity n(%)	31 (68.9)	12 (66.7)	19 (70.4)	0.793
Body Mass Index kg/m ²	24.90 ± 5.74	25.49 ± 4.51	24.50 ± 6.49	0.577
Smoking, n(%)	20 (44.4)	7 (38.9)	13 (48.1)	0.540
SCIG, n(%)	13 (28.9)	5 (27.8)	8 (29.6)	0.893
Diagnostic Delay, months	104.22 ± 91.88	110.56 ± 88.84	100.00 ± 95.28	0.710
Ig dose /mg/month)	400 (200-800)	400 (200-800)	400 (200-800)	0.601
IgG, at diagnosis, (g/dl)	2.75 (0.33-6.90)	3.67 (0.33-6.80)	1.56 (0.33-6.90)	0.016
IgM at diagnosis, (g/dl)	0.31 (0.06-5.99)	0.41 (0.18-5.99)	0.26 (0.06-5.72)	0.164
IgA at diagnosis, (g/dl)	0.25 (0.01-5.02)	0.43 (0.06-5.02)	0.23 (0.01-1.90)	0.022
Neutrophil count (mm ³)	3600 (700-12500)	3320 (700-6300)	3600 (1000-1250)	0.069
Lymphocyte count (mm ³)	1510 (300-8900)	1195 (300-3770)	1700 (400-8900)	0.100
Lymphopenia n (%) (Lymphocyte<1000/mm ³)	13 (28.9)	8 (44.4)	5 (18.5)	0.060
Platelet count (mm ³)	212722.22 ± 93786.00	230074.07 ± 84439.75	187694.44 ± 103273.07	0.130
CD3 (%)	77.50 ± 10.19	74.37 ± 9.15	79.59 ± 10.46	0.092
CD4 (%)	33.64 ± 13.91	35.81 ± 13.64	32.20 ± 14.18	0.401
CD8 (%)	36 (19-74)	33.50 (21-74)	41 (19-74)	0.088
CD4/CD8	1.02 ± 0.78	1.14 ± 0.74	0.94 ± 0.80	0.398
CD19 (%)	7.22 ± 5.75	7.71 ± 5.87	6.90 ± 5.75	0.648
CD16-56 (%)	9.37 ± 6.38	11.03 ± 5.96	8.26 ± 6.51	0.154
CD3(+)CD4(-)CD8(-) T cell	2.00 (0-27)	1.00 (0-11)	2.00 (0-27)	0.542
IgD(-) IgM (-) CD27 (+) B cell	1.20 (0-52)	4.40 (0.1-52)	1.0 (0-20.30)	0.005
CD4(+) CD31(+) CD45RA (+) T cell (%)	16 (0.90-69)	16 (1.90-59.60)	16 (0.90-69)	0.935
TmAb (antithyroid microsomal antibodies), median (min-max)	13.30 (0.1-47.80)	14.60 (0.10- 24.20)	12.90 (1-47.80)	0.410
FEV1≤80%, n (%)	29 (64.4)	11 (61.1)	18 (66.7)	0.703
FEV1, %	71.57 ± 17.15	73.92 ± 16.49	70.00 ± 17.71	0.459
FEV1/FVC, %	98.19 ± 10.01	98.59 ± 9.94	97.93 ± 10.24	0.829
PEF, %	58.99 ± 20.74	60.35 ± 19.60	58.09 ± 21.79	0.725
MEF25-75, %	58.96 ± 24.68	63.62 ± 23.80	55.86 ± 25.20	0.307

Our results showed a higher rate compared to theirs In our study, parental consanguinity was found in 53.3% of patients. Kutukculer et al. and Rivoisy et al. reported that parental consanguinity was associated with a severe phenotype in CVID and this may be the main reason for the high percentages of bronchiectasis in our study group (14, 15). Due to the heterogeneity of the disease, lack of awareness among clinicians concerning primary immunodeficiencies (PID) and the misconception that immunodeficiencies are childhood diseases, delayed

diagnosis is common especially in adult CVID patients (11). The mean diagnostic delay was 104 ± 91.9 months in the present study, which is consistent with Quinti et al.’s report (16). Furthermore, Ardeniz et al. and Musabak et al. also reported similar periods of delayed diagnosis in Turkey (7, 8).

Patients with bronchiectasis had statistically significantly lower IgG and IgA levels and switched memory B cells at the time of diagnosis compared to the patients

Table II: Univariate and multivariate binomial regression analyses demonstrating the relationship between baseline characteristics and bronchiectasis

Variables	Univariants		Multivariants	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
IgG, at diagnosis	4.889 (0.485-0.959)	0.012	1.281 (0.421-1.004)	0.809
IgM, at diagnosis	1.773 (0.505-1.283)	0.108	1.086 (0.576-2.047)	0.798
IgA, at diagnosis	2.559 (0.097-1.235)	0.030	0.408 (0.955-1.113)	0.606
Neutrophil count	1.000 (1000-1001)	0.170	1000 (1.000-1.001)	0.149
Lymphocyte count	1.000 (1.000-1.001)	0.275	1.000 (0.999-1.000)	0.280
Lymphopenia	3.520 (0.918-13.501)	0.067	0.370 (0.073-1.867)	0.229
Platelet count	1000 (1.000-1.000)	0.134	1.000 (1.000-1.000)	0.026
CD3(%)	1.057 (0.989-1.129)	0.103	-	-
CD8 (%)	1.041 (0.992-1.092)	0.106	-	-
CD16-56 (%)	0.932 (0.845-1.027)	0.156	-	-
IgD(-) IgM (-) CD27 (+) B cell (%)	0.848 (0.730-0.984)	0.030	0.853 (0.733-0.991)	0.038

without bronchiectasis. Also, when multivariate analyses were performed, we found that a reduced percentage of switched memory B cells and lower platelet counts are independent risk factors for bronchiectasis. Agematsu et al. reported that in peripheral blood, CD27+ B cells could be classified into two distinct groups: IgD+ CD27+ B cells (non-switched memory B cells) which predominantly secreted IgM, and IgD- CD27+ B cells (switched memory B cells) which synthesized only one of IgG, IgM or IgA (17). Although, decreased switched memory B cells (IgD- IgM- CD27+) in CVID patients are a well-defined characteristic of the disease (18, 19) and CVID has been classified based on memory B cells for over two decades (20), there are conflicting reports on the association between chronic lung disease and decreased isotype-switched memory B cells (21-24). Llobet et al. reported that children with decreased memory B cells had severe complications like bronchiectasis (23). Furthermore, Dectova et al. reported that the memory B cell count was associated with severe respiratory outcomes in CVID (22). Alachkar et al. reported that the percentage of memory B cells but not immunoglobulin concentration was associated with bronchiectasis (25). Our results are similar to this report. Decreased switched memory B cells cause reduced IgG production and less effective pneumococcal antibodies. Therefore, patients have more frequent respiratory tract infections, which can cause higher rates of bronchiectasis in patients with CVID (26). On the other hand, some patients with severe hypogammaglobulinemia

do not suffer from bronchiectasis. Non-switched memory B cells can still synthesize sufficient anti-pneumococcal IgM and these antibodies may protect the patient from the development of bronchiectasis (26).

Bronchiectasis is not only associated with recurrent sinopulmonary infections, but is also proof and indication of other inflammatory conditions (27). Kellner et al. reported that CVID patients with bronchiectasis had more autoimmune complications such as autoimmune hematologic diseases, hepatomegaly, splenomegaly and lymphadenopathy than CVID patients without bronchiectasis (28). Regulatory T cells (T-regs) play an important role in the preservation of immune homeostasis (29). Romberg et al. reported that a decreased number of T-regs, reduced T-reg function and an increased number of follicular T cells in the germinal center of lymph nodes might correlate with fewer isotype switched memory B cells (30). Therefore, reduced T-reg function may contribute to the development of bronchiectasis. Although some monogenic immunodeficiencies such as PI3KD (A phosphoinositide 3-kinase delta) gain of function mutation may lead to bronchiectasis, the genetic analysis of any of our patients has not been concluded yet.

Although thrombocytes may not have a direct association with chronic lung disease, the relationship between these two conditions in CVID patients has been shown in many studies (6, 31). In this patient group, low platelet counts may be an indicator of splenic sequestration due to

splenomegaly, and/or may be an expression of increased immune dysregulation and autoimmunity. Maglione et al. found that thrombocytopenia was significantly associated with chronic lung disease in patients with CVID (32). In the current study, we found that platelet counts were lower in patients with bronchiectasis than in those without bronchiectasis, and low platelet counts were independent risk factors for the development of bronchiectasis. Although infections are the main cause of bronchiectasis, there are other inflammatory conditions in addition to infections in the continuation of bronchiectasis (27) and presumably, decreased platelet count in CVID patients is a reflection of these additional inflammatory conditions.

Our study has some limitations, such as a small study population, a single center experience and cross-sectional design. Also, we could not analyze the relationship between the severity of bronchiectasis and other immunological parameters.

CONCLUSION

In conclusion reduced percentage of switched memory B cells and reduced platelet counts are independent predictors for the development of bronchiectasis, and therefore, patients with CVID who have decreased switched memory B cells and reduced platelet counts require close clinical monitoring to detect and treat complications associated with bronchiectasis at an early stage.

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CONFLICT of INTEREST

None.

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