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Original Article

Comparison of Clinical Manifestations, Immunological Analyses between LRBA and CVID Patients: A Longitudinal Study

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Abstract

Background: Common variable immunodeficiency (CVID), is generally recognized as the most frequent type of Symptomatic primary immunodeficiencies (PID). Mutations in lipopolysaccharide-responsive beige-like anchor protein (*LRBA*) gene, are the most common genetic alterations amongst CVID patients. To date, there are no published studies to compare clinical and immunologic features of LRBA-deficient patients with those who do not harbor any known genetic mutations. Therefore, this study aims to compare the clinical manifestations and laboratory findings of Iranian patients with LRBA-deficiency and CVID with no known genetic alterations.

Methods: We performed a longitudinal study on patients who had been diagnosed with CVID. Demographic and clinical features were obtained via the databank of the Iranian Registry of Primary Immunodeficiencies, and the direct interviews with patients. To assess the presence of *LRBA* or other genetic mutations, whole-exome sequencing (WES) was used. Immunologic characteristics of patients were evaluated using flow cytometry, nephelometry, and conventional blood counts. The current study is conducted at Tehran's Children Medical Center and is approved by the ethics committee of Tehran University of Medical Sciences.

Results: Between March 2013 and October 2019, we enrolled 30 patients with LRBA-deficiency and 13 patients with CVID, who had no identified genetic mutations. Regarding clinical features, there were no significant differences for the prevalence of infections at different sites (lung, sinuses, and middle ear) among the two groups (all $P > 0.05$). However, the incidences of autoimmune disorders and enteropathy were significantly higher among LRBA-deficient cases ($P < 0.001$). In serum levels of immunoglobulins, there were significant differences for IgG and IgM between the two groups (P of 0.014 and 0.004, respectively); however, this was not seen for IgA and IgE levels. Likewise, we did not see any significant differences for the cluster of differentiation (CD) markers between the two groups (all $P > 0.05$).

Conclusion: Compared to the CVID patients with no identified genetic mutations, LRBA-deficient patients have a significantly greater chance of parental consanguinity and developing autoimmune disorders and enteropathy, and have significantly higher values of serum IgG and IgM. The rate of infectious complications and other basic laboratory features, do not show significant differences between the two groups.

Keywords: Common Variable Immunodeficiency; Lipopolysaccharide-Responsive Beige-Like Anchor Protein; Immunodeficiency; Autoimmunity; Enteropathy

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Introduction

Primary immunodeficiencies (PID), comprise a heterogeneous group of inherited disorders characterized by defects mainly in cellular, humoral, or innate immune system or their combinations. Despite the rarity, delineation of pathophysiologic and clinical aspects of these disorders can considerably enhance our understanding of various functions of the immune system and further aid in the treatment of other immune-related diseases (e.g., autoimmune and infectious diseases)(1). First described in 1953, the common variable immunodeficiency (CVID) is generally considered as the most common symptomatic PID, and is characterized by the onset of symptoms in the second and third decades of life, with recurrent sinopulmonary and gastrointestinal (GI) infections, non-caseous granuloma formation, increased risk of developing autoimmune disorders and malignancies, and hypogammaglobulinemia (2).

To date, several genetic alterations have been identified, as the causatives of the development of CVID. There are several well-recognized autosomal recessive (e.g., *or* TNF receptor superfamily member 13C (TNFRSF13C) or BAFF receptor (BAFFR) ICOS, and CD19) and autosomal dominant (e.g., TNF receptor superfamily member 13B)TNFRSF13B (or transmembrane activator and CAML interactor [TACI]) mutations linked to the development of CVID; however, these are present in less than 20% of the cases (2, 3). Mutations in *LRBA,* are examples of more recently discovered genetic alterations among CVID patients. In fact, LRBA mutations comprise one of the most commonly seen genetic alterations among them (4). Lipopolysaccharide responsive beige-like anchor protein gene, is located on chromosomal region 4q31 (5), and although its exact physiologic roles are not elucidated yet, it is postulated that it is involved in apoptosis and autophagy signaling pathways, and is conducive to the maintenance of intra-cellular cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pools (6). Biallelic mutations of *LRBA* are seen in patients with CVID-like (5, 7) and ALPS-like (6, 7) syndromes.

There are several reports on patients who have CVID phenotype and harbor different genetic alterations (as mentioned earlier) to delineate their clinical and laboratory features and further reveal possible differences. Although there are several available studies in the literature describing patients with LRBA deficiency, but to date, there has been no report on the comparison of the clinical manifestations and laboratory findings between such cases and CVID patients with no genetic alterations. Hence, the aim of this study is to compare clinical and laboratory manifestations of these two groups in an Iranian cohort of PID patients and further hypothesized that, owing to the heterogeneous nature of CVID, there will be meaningful differences between these two groups of patients.

Methods

Study design and participants

This longitudinal study is conducted to Tehran's Children Medical Center. Tehran University of Medical Science's ethics committee approved this study, and informed consents were obtained from patients and/or their parents.

This study was aimed to compare clinical and immunological features of patients who harbor biallelic LRBA mutations with CVID patients with no identified mutations. Hence, our inclusion criteria were the presence of LRBA mutations (LRBA deficient group) or clinical manifestations of CVID (according to the standard criteria (8)), without any identified genetic mutations (CVID group, assessed by WES). The exclusion criterion was the patient's or patient's parent's dissatisfaction to participate in the study. All the enrolled patients in this study are registered at the Iranian Registry of Primary Immunodeficiencies (9).

Clinical assessment

Demographic data, including age, sex, date of the first presentation, date of the definitive diagnosis, and parental consanguinity, were obtained from the databank of the Iranian Registry of Primary Immunodeficiencies. The incidence of infectious, autoimmune, and neoplastic disorders, the presence of granulomas, splenomegaly, lymphadenopathy, and other related physical findings were recorded using registry data and direct contact with patients, including clinical interviews and physical examination.

Immunologic and laboratory assessment

The expression of CD3, CD4, CD8, and CD19 on immune cells was assessed by flow cytometry.

Serum IgA, IgE, IgG, and IgM levels, were analyzed by nephelometry. All patients underwent WES, to evaluate the presence of any known genetic mutations. The detailed methods of conducting the abovementioned tests are provided elsewhere (10).

Statistical analysis

Data in this study are presented as frequencies (count and percentage), mean ± standard deviation (SD), and median with Interquartile Range (IQR), as appropriate. The Fisher's exact and X^2 tests were used for 2 by 2 contingency data, and the student's t-test and the Mann-Whitney U test were used to compare continuous parametric and nonparametric variables, respectively. Statistical analyses were conducted using SPSS Statistics for Windows, Version 27.0 (IBM Corp, Armonk, NY, USA). A P-value < 0.05 was considered statistically significant.

Results

Demographic features

Between March 2013 and October 2019, 43 patients enrolled in this study; 30 were assigned to the LRBA-deficient group, and the remaining 13 were assigned to the CVID group. The median age at the time of the first presentation, was 1.5 years (0-35.9) for LRBA-deficient, and four years (0-28) for the CVID group (P > 0.05). The median

Table 1. Basic demographic characteristics of patients with LRBA-deficiency and CVID without identified genetic mutations

Demographic variable	LRBA-deficient (n=30)	CVID (n=13)	*P*-value
Median age at the time of diagnosis (range)	14.5 (0-44)	14 (3-41)	0.39
Median age at the time of first presentation (range)	1.5 (0-35.9)	4 (0-28)	0.25
Median diagnosis delay time (range)	4.54 (0-32)	7 (0-36)	0.7
Median duration of the disease (range)	12.45 (0-33)	9 (1-40)	0.2
Consanguinity of parents	96.55%	58.33%	**0.005**
Female/male ratio	15/15	7/6	1

LRBA, lipopolysaccharide-responsive beige-like anchor protein; CVID, common variable immunodeficiency.

Table 2. The initial clinical picture of patients with LRBA-deficiency and CVID without identified genetic mutations

First clinical presentation	LRBA-deficient (n=30)	CVID (n=13)	*P*-value
Infectious disorder n (%)	12 (40)	6 (46.1)	0.75
• Pneumonia, n (%)	7 (23.3)	3 (23.1)	1
• Sinusitis, n (%)	2 (6.7)	3 (23)	0.15
• Respiratory tract infection, n (%)	2 (6.7)	0 (0)	1
• Otitis media, n (%)	1 (3.3)	0 (0)	1
Autoimmune disorders n (%)	5 (16.7)	0 (0)	0.3
• Immune thrombocytopenic purpura, n (%)	3 (10)	0 (0)	0.54
• Autoimmune hemolytic anemia, n (%)	2 (6.7)	0 (0)	1
Chronic diarrhea, n (%)	6 (20)	2 (15.4)	1
Failure to thrive, n (%)	2 (6.7)	0 (0)	1
Mesenteric adenitis, n (%)	1 (3.3)	0 (0)	1
Allergic dermatitis, n (%)	1 (3.3)	0 (0)	1
Asthma, n (%)	1 (3.3)	0 (0)	1
Fever, n (%)	1 (3.3)	1 (7.7)	0.52
Craniofacial malformation, n (%)	1 (3.3)	0 (0)	1
Others/missing, n (%)	0 (0)	4 (30.7)	-

LRBA, lipopolysaccharide-responsive beige-like anchor protein; CVID, common variable immunodefici

Table 3. Clinical manifestations of patients with LRBA-mutations and CVID without any identified mutations

Experienced clinical syndrome	LRBA-deficient (n = 30)	CVID (n = 13)	*P*-value
Splenomegaly, n (%)	18 (60)	4 (30.8)	0.104
Hepatomegaly, n (%)	12 (40)	2 (15.4)	0.164
Organomegaly, n (%)	18 (60)	4 (30.8)	0.104
Lymphadenopathy, n (%)	9 (30)	5 (38.5)	0.726
Autoimmunity, n (%)	21 (70)	0	**< 0.001**
• ITP, n (%)	11 (36.7)	0	0.019
• AIHA, n (%)	7 (23.3)	0	0.082
• AIE, n (%)	4 (13.3)	0	0.297
• JIA, n (%)	4 (13.3)	0	0.22
• IBD, n (%)	4 (13.3)	0	0.297
• AIT, n (%)	2 (6.7)	0	1
• Celiac, n (%)	2 (3.3)	0	1
• MG, n (%)	1 (3.3)	0	1
• Evans syndrome, n (%)	1 (3.3)	0	1
• MS, n (%)	1 (3.3)	0	1
• AIH, n (%)	1 (3.3)	0	1
• Vitiligo, n (%)	1 (3.3)	0	1
• Type 1 diabetes, n (%)	1 (3.3)	0	1
Otitis media, n (%)	14 (46.7)	5 (38.5)	0.743
Sinusitis, n (%)	15 (50)	8 (61.5)	0.526
Pneumonia, n (%)	19 (63.3)	6 (46.2)	0.332
Enteropathy, n (%)	20 (66.7)	1 (7.7)	**0.001**
Other infectious complications	21 (70)	N/R	
• Bronchiectasis	11 (36.7)	N/R	
• Candidiasis	9 (20.9)	N/R	
• Septic arthritis	5 (11.6)	N/R	
• Meningitis	4 (9.3)	N/R	
• Conjunctivitis	4 (9.3)	N/R	
• Septicemia	2 (4.7)	N/R	
• Skin infections	2 (4.7)	N/R	

LRBA, lipopolysaccharide-responsive beige-like anchor protein; CVID, common variable immunodeficiency; ITP, immune thrombocytopenic purpura; AIHA, autoimmune hemolytic anemia; AIE, Autoimmune Enteropathy; JRA, juvenile idiopathic arthritis; IBD, inflammatory bowel disease; AIT, Autoimmune thyroiditis; MG, myasthenia gravis; MS, multiple sclerosis; AIH, Autoimmune hepatitis; N/R, not reported.

age at the time of diagnosis, was 14.5 years (0-44) for LRBA-deficient, and 14 years (3-41) for the CVID group (P > 0.05). The female/male ratio was 15/15, and 7/6 for LRBA-deficient and CVID patients, respectively **(Table 1)**. About 97% (28/29) of LRBA-deficient, and 58% of CVID patients had positive parental consanguinity (P = 0.005).

Clinical presentation

The first clinical presentation of each group is illustrated in (**Table 2**). In brief, 36.7% of LRBA-deficient cases had an infectious disease as their first clinical symptom, while chronic diarrhea and autoimmunity were the first diagnoses in 20% and 16.7%, respectively. For the CVID group, 46.2% had experienced an infectious disease as their first

Table 4. laboratory and immunologic characteristics of patients with LRBA-mutations and CVID without any identified mutations

Laboratory parameter	LRBA-deficient (n = 30)	CVID (n = 13)	*P*-value
Leukocyte count (cells/mL) (IQR)	9202 (5285-11475)	8033 (5925-11052)	0.8
Lymphocyte count (cells/mL) (IQR)	3267 (1657-4082)	2716 (1695-3820)	0.7
Hemoglobin level (g/dL) (IQR)	11.85 (10.5-13)	12.3 (10.8-12.6)	0.6
Total CD3 count (cells/mm^3) (IQR)	2306 (777-2741)	2379 (1422-2638)	0.3
Percentage of $CD3^+$ T-cells (IQR)	67.78 (57.25-79.75)	75.51 (61.07-85)	0.2
Total CD4 count (cells/ mm^3) (IQR)	969 (284-1156)	1293 (540-1836)	0.2
Percentage of $CD4^+$ T-cells (IQR)	31.09 (24.75-36.37)	37.43 (19-49)	0.2
Total CD8 count (cells/mm^3) (IQR)	1142 (251-1430)	1147 (780-1386)	0.2
Percentage of $CD8^+$ T-cells (IQR)	34.34 (20.5-47.5)	42.24 (30-59)	0.19
Total CD19 count (cells/ mm^3) (IQR)	543 (43-419)	209 (75-329)	0.9
Percentage of $CD19^+$ T-cells (IQR)	13.63 (4-14)	7.13 (1.69-11.97)	0.31
IgA (mg/dL) (IQR)	36.96 (3-49.5)	47.8 (2-30)	0.7
IgE (mg/dL) (IQR)	7.92 (0-5.5)	5.42 (1-10)	0.424
IgG (mg/dL) (IQR)	477.82 (135.25-668.75)	194.54 (18-224)	**0.014**
IgM (mg/dL) (IQR)	79.96 (18.25-118.25)	17.6 (5-20)	**0.004**

LRBA, lipopolysaccharide-responsive beige-like anchor protein; CVID, common variable immunodeficiency; IQR, inter-quartile range; ml, milliliter; dl, deciliter; CD, cluster of differentiation; Ig, immunoglobulin.

clinical manifestation, and chronic diarrhea had occurred in 15.4%. Of note, none of these patients had experienced an autoimmune disorder as the initial symptom of the disease.

Regarding infectious complications, the only reported disorders for both groups were otitis media, pneumonia, and sinusitis. The first two mentioned infections were more prevalent in the LRBA-deficient group, while sinusitis was more common among patients of the CVID group. However, none of these differences were statistically significant. Among LRBA-deficient cases, 21 (70%) had at least one infectious disorder other than the abovementioned ones, with bronchiectasis (the consequence of recurrent pneumonia) as the most prevalent disorder (**Table 3**). However, since such infections had not been recorded for CVID cases, further statistical analyses were not possible. To date, none of the patients in these two cohorts have been diagnosed with any type of malignancy.

Hematologic and immunologic features

There were no statistically significant differences between the two groups regarding hemoglobin levels, leukocyte, and lymphocyte counts (**Table 4**). Likewise, basic immunologic assessments (IgA, IgE, CD3, CD4, CD8, and CD19 levels), were similar between the two groups; the only significant differences were observed for IgM and IgG levels, which were lower among patients of the CVID group ($P < 0.004$ and $P < 0.014$, respectively).

Discussion

Patients with CVID, represent a wide variety of clinical and immunologic symptoms. One of the main culprits for this heterogeneity, is the lack of definite, limited-number genetic mutations as the underpinnings of the disease (2). Owing to recent advances in whole-genome sequencing, more genetic alterations are being identified. For example, in a cohort study, 54% of Iranian and 36% of Swedish CVID patients have been harboring relevant genetic mutations (4).

One of such novel mutations is identified for the *LRBA* gene. Cases with this genetic alteration were first reported in 2012 (5, 7). One of these reports, described three patients with CVID-like (one with recurrent infection and another one with Autoimmune Hemolytic Anemia (AIHA) and Idiopathic Thrombocytopenic Purpura

(ITP)), and two with inflammatory bowel disease (IBD)-like syndromes (7). The second study, described five cases with CVID symptoms, including recurrent infections, as well as ITP and/or AIHA, in all except one (5).

Following these reports, other studies were aimed to describe clinical and immunologic features of LRBA-deficient cases. For instance, a report of 31 LRBA-deficient patients (6), found the presence of chronic diarrhea, autoimmune disorders, organomegaly, respiratory infections (each 61%), hypogammaglobulinemia (58%), and growth retardation (42%), as the commonest clinical manifestations. Besides, about 70% of the cases, had experienced their first disease presentations at ages under five years. The authors of this study, have further categorized the manifestations into three groups, named enteropathy, autoimmunity, and immunodeficiency phenotypes, with the presence of at least two in most cases. Notably, as evidenced by another report (11), this study has found no genotype-phenotype correlations for *LRBA* mutations (6).

In another study on 15 patients who had *LRBA,* mutations and presentations consistent with CVID or ALPS (12), splenomegaly (93%), autoimmune cytopenia and increased double-negative T-cells (each 80%), decreased B-cell count (60%), chronic diarrhea, and lower respiratory tract infections (each 53%), were the most common findings (12). Another study on 22 cases with *LRBA* mutations (nine with CVID and four with ALPS-like syndrome), has reported a low plasmablast count (92%), presence of organomegaly (86%), decreased T-reg counts (73%), recurrent infections (71%), defective response to antibodies (67%), enteropathy (59%), hypogammaglobulinemia (57%), AIHA (55%), and ITP (50%), as the most prevalent clinical and immunologic features. Interestingly, the mean age at the time of presentation of first symptoms, has been as low as four years, which is in concordance with reports of other studies (13).

Regarding CVID, its clinical and immunologic features, demonstrate substantial differences with LRBA-deficiency in some respects. For example, the age at the time of appearance of first symptoms, is higher for CVID, and according to most studies, lies in the third decade of life (2). More ever, organomegaly, autoimmune disorders, and IBD-like symptoms occur with fewer frequencies among CVID patients (2, 14). A recent meta-analysis on 8521 CVID patients, has found the prevalence of such manifestations as following: lymphadenopathy (27%), splenomegaly (13%), IBD (11%), autoimmune cytopenia (10%), and ITP (6%) (14).

Owing to the widespread application of genetic testing, the importance of *LRBA* mutations among CVID cases has become more evident. In fact, in Abolhassani et al. study, LRBA mutations have been the most frequently seen genetic alteration among Swedish and Iranian cohorts of CVID (4). Although the exact mechanisms by which LRBA-deficiency leads to immune dysregulation are not known, it is postulated that CTLA-4 has a central role. As mentioned earlier, LRBA contributes to the post-translational regulation and maintenance of CTLA-4 on the membrane of T-cells, especially regulatory subtypes. Decreased surface expression of the CTLA-4 on Treg cells, can lead to the disinhibited immune responses, which culminates in both autoimmunity and immune deficiency (15, 16). The demonstration of similar clinical symptoms to that of LRBA-deficiency (AIHA, pneumonitis, hypogammaglobulinemia, and lymphadenopathy) (15, 17), and clinical improvement after the application of a CTLA-4 fusion drug (abatacept) (18), further corroborates the abovementioned hypothesis.

In our study, the mean age at the time of the first presentation, was three years for LRBA-deficient, and 5.7 years for the CVID group. Despite not being statistically significant, it is in concordance with observations of other authors. As mentioned before, the first manifestations of CVID, usually becomes evident in the third decade of life, but in our cohort, the median age has been four years (range, 0-28). This might be explained by the rigorous clinical examination, of children who have had a sibling with PIDs. However, the reason behind the earlier onset of symptoms among LRBA-deficient patients is not elucidated yet, and mandates more basic science research. Also, in our cohorts and due to the AR inheritance of *LRBA* mutations, there was a significantly higher proportion of parental consanguinity among LRBA-deficient cases.

The clinical and immunological features

of LRBA-deficient patients of our study, are generally in concordance with the descriptions of previous reports. The most common clinical manifestations of our LRBA-deficient cohort, were autoimmune disorders (70%), enteropathy (67%), pneumonia (63%), and organomegaly (60%). In contrast, none of the CVID cases had the demonstration of autoimmune disorders, and the only manifestation with a frequency of more than 50%, was sinusitis. Notably, compared to other patients with CVID, cases of our cohort had a greater prevalence of lymphadenopathy and organomegaly and a decreased incidence of autoimmune disorders. Considering the small sample size of this group, such differences might also stem from the fact that most previous studies on CVID patients have not divided them based on genetic alterations.

Most reports on LRBA-deficiency, have mentioned autoimmune disorders as the foremost symptoms. However, in our study, infections (40%) were the most common incipient disorders, while autoimmune disorders were evident in just five cases (17%). Furthermore, among these five patients, three had ITP, and the other two cases had AIHA, which differs from the observations of other authors, as they have identified IBD-like syndromes and enteropathy, as the commonest incipient autoimmune disorders. Further identification of initial presentations is prudent, as some have even recommended genetic testing of LRBA mutations for children with IBD and hematologic autoimmune disorders (16). Regarding differences in overall clinical manifestations of LRBA-deficient and CVID cases, although no autoimmune disorders have been present among the latter group, no statistically significant difference was found, probably due to the small sample size of the CVID group.

Although low serum IgG level is required for the diagnosis of CVID, not all patients with LRBA mutations fulfill this criterion (12, 13). In our study, almost all patients had low serum IgG and IgA levels, with significantly lower values for IgM and IgG among CVID patients. It is still not clear whether the patients with LRBA mutations have lower immunoglobulin levels, and what subtypes are generally decreased. Further studies with the enrollment of healthy subjects as controls, are required to reach robust conclusions. Other conventional immunologic parameters, including leukocyte, lymphocyte, CD3, CD4, CD8, and CD19 cell counts, do not tend to show any aberration from normal values (5, 6, 13). Likewise, most cases of our cohort, exhibited normal values for such parameters.

There are several limitations to the present study. The number of cases with CVID with no identified genetic alterations was 13, and there were missing values for some clinical and laboratory values. In addition, laboratory studies were limited to conventional testing, and more complex assays (e.g., Tregs, switched and non-switched memory B-cells, transitional B-cells, and plasmablast counts), have not been performed for patients.

Conclusion

Compared with the CVID patients without genetic mutations, LRBA-deficient patients, exhibit relevant clinical phenotype at lower ages, and have a significantly greater probability of having consanguineous parents and developing autoimmune disorders and enteropathy. Except for IgG and IgM serum levels, there are no significant differences between these two groups regarding basic immunologic and laboratory studies.

Conflict of interest

The authors of this study declare no conflicts of interests.

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