Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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ORIGINAL ARTICLE

OPEN ACCESS

Application of the diagnostic criteria for Common Variable Immunodeficiency in resource-limited settings

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Received 1 September 2021; Accepted 4 May 2022
Available online 1 July 2022

KEYWORDS
Common variable immunodeficiency;
CVID diagnosis;
ESID registry working definitions;
inborn errors of immunity;
primary immunodeficiency diseases

Abstract
Introduction: Common variable immunodeficiency (CVID) is the most prevalent symptomatic humoral deficiency; however, its heterogeneous presentation makes the diagnosis difficult. The present study is aimed to verify the CVID diagnostic criteria as established by the European Society for Immunodeficiencies in 42 CVID patients from our outpatient clinic.
Methods: Information was collected from their medical records and when needed, lymphocyte subpopulations in peripheral blood (PB) were performed by flow cytometry.
Results: All the patients fulfilled the clinical working definition for CVID and showed decreased serum IgG and IgA at diagnosis. Over two-thirds of the patients had decreased memory B cell percentages. However, the remaining patients exhibited other quantitative B cell defects in PB. Evaluation of vaccination responses was only found in 13 records and 69% were not responsive. None of the patients were subjected to vaccination studies to both, T-cell dependent and independent antigens. The two required tests to evaluate T cell responses were performed in 84.2% of the patients and reported normal. Without the support of third-party payers, only 34.2% of our patients would have completed the required evaluations.
Conclusions: Further efforts are needed to speed up CVID diagnosis in low-resourced settings, increasing the availability of the required resources and optimizing the healthcare supply chain.

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https://doi.org/10.15586/aei.v50i4.496

Introduction

Predominantly antibody deficiencies (PAD) are inborn errors of immunity (IEI) that affect serum antibody production and B cell numbers and their function. Although IgA deficiency is the most common of these defects, it is usually asymptomatic.[1] However, common variable immunodeficiency (CVID), is considered as the most common symptomatic PAD,[2] with an estimated prevalence of 1:100,000–10,000 in the general population.[3] According to a study about the burden of disease in 2700 CVID patients, this condition is among the top 10 disability health problems in Europe.[4] Although considered a diagnosis of exclusion until the cause of the immune abnormalities is elucidated, CVID is defined as a syndrome of increased susceptibility to recurrent infections accompanied by hypogammaglobulinemia and poor response to vaccination. However, diagnosis is very challenging for several reasons. First, CVID clinical presentation is very heterogeneous with non-infectious comorbidities occurring in about two-thirds of the patients, also representing the first manifestation of the disease.[5] Second, serum immunoglobulin (Ig) levels exhibit normal fluctuations over time due to environmental factors, especially in children. Finally, responses to vaccination also vary depending on the vaccine reactivity and the genetic background of the population. Thus, major efforts have been made to harmonize criteria that facilitate diagnosis.[6–13]

In 1999, the Pan- American Group and the European Society for Immunodeficiency (PAGID and ESID, respectively), agreed upon the diagnostic criteria for CVID. They classified patients with compatible clinical features, absent isohemagglutinins and/or poor response to vaccines, in possible and probable cases. This mainly depended on whether the decrease in serum IgG and IgA is accompanied by a decrease in IgM, after the exclusion of secondary causes of hypogammaglobulinemia.[12] To carefully search for other signs of immune system failure, rule out CVID-like genetic defects and improve the characterization of the non-infectious comorbidities, Ameratunga et al.[10,11] revised those criteria and recommended the inclusion of other laboratory and histological abnormalities in the diagnostic workflow. In 2014, ESID published a list of criteria for a probable diagnosis of CVID cases (at https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria) which was complemented in 2019.[9] The quantification of switched memory B cells was added as an alternative to the assessment of vaccination responses or isohemagglutinin titers. Also, they included the evaluation of the T cell branch of immunity to improve decision-making for timely adaptation of immunization schemes and prevention/surveillance of intracellular or opportunistic infections in patients with combined immunodeficiencies.

However, how applicable are ESID CVID criteria in countries with high economic inequalities and complex access to health care? In Colombia, for example, the coverage of this system is considered optimal but social, economic, and logistic determinants constantly deteriorate patients' quality of care.[14–16] As suggested by the number of reported patients and the participating centers in the Latin American Society for immunodeficiencies (LASID) registry (available at lasidregistry.org), great differences exist among these countries for accessing integrated routes that facilitate IEI diagnosis. This aspect is also emphasized in recent reports.[17] In Africa, Erjaee et al.[18] reviewed the status of the IEI prevalence, geographical distribution, and diagnostic challenges. They stated that specialized laboratory tests such as lymphocyte subpopulation and proliferation studies, among others, are only available in a very limited number of referral centers in this continent. They face challenges in the diagnosis and management of these patients due to limited expertise and financial constraints. Also, a case-based discussion from a CVID patient in Kazakhstan outlined the barriers to the diagnosis of IEI in less-resourced settings, where access to specialized medical care is more problematic.[19] Despite these reports, there is a lack of information about the fulfillment of the diagnostic criteria for CVID in low-resourced settings.

The present study is aimed to verify the fulfillment of the ESID criteria for CVID[9] in a census of 42 patients, attending our outpatient clinic for immunological disorders in Medellín, Colombia. Among all our results, the following three results stand out: first, vaccination studies, T cell proliferation, and naïve T cell subsets were the less documented parameters in the clinical records. Second, most of the required evaluations were completed only with the support of research grants. Lastly, abnormalities in B cell subpopulations in our CVID patients extended beyond the decrease in switched-memory B cells. The first two findings suggest that further effort is needed to guarantee the timely supply of vaccines and tests for the evaluation of CVID patients in our settings. The third finding indicates that harmonization is still needed in the definition of the B-cell abnormalities in CVID.

Materials and Methods

Patient selection

All patients recruited belonged to the CVID census and were at follow-up visits at Grupo de Inmunodeficiencias Primarias, Universidad de Antioquia UdeA, Medellín, Colombia. The information needed was either collected from their medical records or obtained by phone calls. This protocol was classified as possessing "no greater than minimal risk" by the Institutional Review Board (IRB) at Facultad Nacional de Salud Pública, Universidad de Antioquia, Medellín, Colombia (IRB approval 112, November 20, 2014). All the patients recruited, accepted, and signed the informed consent or assent form.

Immunological tests

Clinical records provided us with information about the initial values of serum Ig, immunophenotyping, evaluation of responses to vaccination, and T-cell proliferation. When immunophenotyping was not available in the clinical records, PB was collected in ethylenediaminetetraacetic acid (EDTA)-anticoagulated Vacutainer® tubes (Becton Dickinson, BD, Franklin Lakes, NJ). Total white cell counts per mL blood were performed by light microscopy, using glacial acetic acid 0.3% (J. T. Baker, Fisher Scientifics,

Phillipsburg, NJ). Then, red blood cells were lysed using 1 mL of FACS™ lysing solution 1X (BD) for 10 min at room temperature, followed by two washes with Dulbecco's Phosphate Buffered Saline (DPBS) 1X (GIBCO – Thermo Fisher Scientific, Waltham, MA). Thereafter, specific markers in the leukocytes were targeted by using fluorescent-labeled monoclonal antibodies, as follows: total and naïve T helper cells were characterized by using antibodies against CD45 (Clone HI30), CD3 (Clone UCHT1), CD4 (clone RPAT4), CD8 (clone RPAT8), CD45RA (clone HI100), and CCR7 (clone 3D12). To evaluate the B cell compartment, we used antibodies against CD19 (clone HIb19), CD21 (Clone BLY4), CD27 (Clone M-T271), IgD (Clone IA6-2), CD38 (Clone HIT2), and CD24 (ML5). The acquisition was performed in the FORTESSA LSR (BD) and analyzed in the software Flow Jo version 9.9.6 (https://www.flowjo.com/solutions/flowjo/downloads/v9).

Statistical analysis

Descriptive statistics were used to analyze the qualitative variables. This is presented as the percentages and absolute frequencies of the patients with specific clinical manifestations or fulfilling the criteria, related to the total number of patients. Venn diagrams were drawn at https://miro.com/app/dashboard/

Results

Clinical characteristics of the patients included in this study

From the CVID census, we included 42 patients (27 were male, 15 were female; 1:1.8 female to male ratio) with the availability of the clinical records. Four patients were deceased at sample collection.

The median age at recruitment was 29.5 years (Min–Max = 6–84). The median age at onset of symptoms was 6 years (Min–Max = 2–20). Thirty of our patients had an early onset disease, with initial symptoms either in infancy or early adulthood. However, the median age at CVID diagnosis was 22 years (Min–Max = 9–45) and the median diagnostic delay of 11.2 years (Min–Max= 0–49).

As shown in Table 1, the most affected area in all patients was the respiratory tract. The gastrointestinal tract was also frequently affected by recurrent infections. From the respiratory tract infections, pneumonia was the condition most commonly observed (26/42, 61.9%) and among those patients, bronchiectasis was reported in approximately one-fifth (9/42, 21.4%).

From the non-infectious comorbidities, autoimmunity was the most frequent in this group of patients (13/42, 30.9%), followed by polyclonal lymphocytic infiltration.

Table 1 Clinical characteristics of the CVID patients included in this study.

Clinical features documented in the clinical records		%	Absolute frequency
Anatomic site for the first symptom	Respiratory tract	57.1	24/42
	Skin and mucous membranes	14.3	6/42
	Gastrointestinal tract	11.9	5/42
	Genitourinary tract	4.8	2/42
	Nervous system (meningitis)	2.4	1/42
	Organomegalies	4.8	2/42
Type of infection during the disease progression	Respiratory tract	85.7	36/42
	Pneumonia	61.9	26/42
	Bronchiectasis	21.4	9/42
	Skin and mucous membranes	45.2	19/42
	Gastrointestinal tract	50	21/42
	Genitourinary tract	11.9	5/42
	Nervous system (meningitis)	9.5	4/42
	Hepatitis	9.5	4/42
	Mastoiditis/parotitis	9.5	4/42
	Warts	7.1	7/42
	Chickenpox infection	16.7	7/42
	Other*	14.3	6/42
Anatomic site for recurrent infections	Respiratory tract	59.5	25/42
	Skin and mucous membranes	2.4	1/42
	Gastrointestinal tract	28.6	12/42
Non-infectious comorbidities	All non-infectious comorbidities	52.4	22/42
	Autoimmunity	30.9	13/42
	Polyclonal lymphocytic infiltration	21.4	9/42
	Enteropathy	14.3	6/42
	Malignances	11.9	5/42

*Measles, septic arthritis, sacroiliitis, Herpes Zoster, histoplasmosis.

Fulfillment of the clinical features compatible with CVID

The fulfilment of all the ESID criteria in the group of patients presented here is shown in Table 2. First of all, ESID establishes that CVID patients must have at least one of the following working definitions for the clinical diagnosis: increased susceptibility to infection, autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation, or an affected family member with antibody deficiency. At diagnosis, we found that 41/42 (97.6%) of our CVID patients exhibited increased susceptibility to infections and only one hepato-splenomegaly, compatible with unexplained polyclonal lymphoproliferation. Only 10/39 (25%) of our patients reported other family members affected with antibody deficiencies. Among them, three were siblings and seven were first cousins. Three patients have no information about the family history

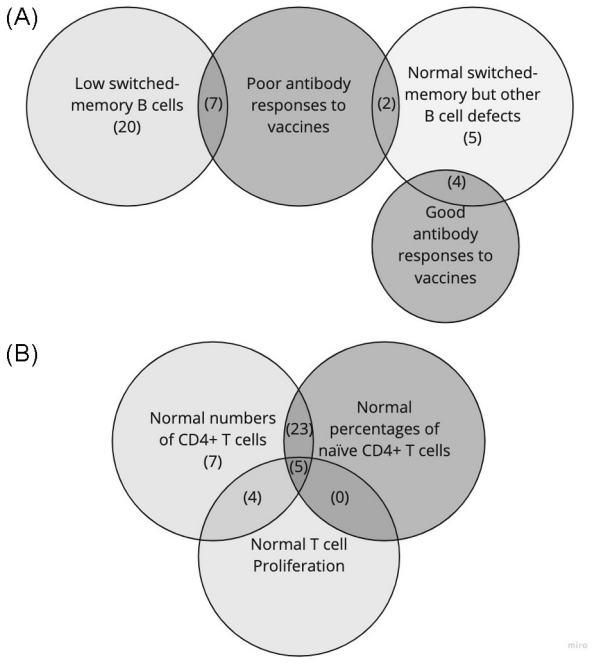

Figure 1 Evaluation of humoral and celular immune responses in our CVID census. Numbers in parentheses indicate the number of patients with the corresponding feature.

of primary immunodeficiencies in the clinical records. Based on these data, all the CVID patients included here fulfilled the first set of criteria included in the ESID working definition for CVID.[7]

Decrease in serum Ig and evaluation of B cell numbers and function

ESID establishes that the clinical manifestations as defined above must be accompanied by a marked decrease in the serum IgG and IgA. All our CVID patients exhibited reduced serum IgG and IgA levels. Also, 70% showed a concomitant decrease in serum IgM (Table 2). However, these measurements were always documented as having been performed only once, previous to the initiation of the subcutaneous or intravenous immunoglobulin replacement therapy (SCIG or IVIG, respectively).

In addition, CVID patients must exhibit either poor antibody responses to vaccination, low isohemagglutinin titers or low memory B cells in PB. No evidence of isohemagglutinin analyses was found. Only 13/42 (31%) of clinical records contained laboratory reports about responses to vaccination (Table 2 and Venn diagram A from Figure 1). As specified in Table 3, those records showed that two out of four patients in whom these tests were performed had deficient responses against the 23-valent pneumococcal polysaccharide vaccine (Pneumo®23). Three documented only evaluation of antibody responses against the diphtheria toxoid and another one only against Hepatitis B; however, none of them responded to immunization. Three patients presented vaccination reports only against Rubella and all were non-responders. Finally, two patients were evaluated for serum antibody responses against Rubella and Hepatitis B and one each turned out to be unresponsive only to one of the evaluated vaccines. These patients were therefore considered responders. Thus, nine out of 13 patients did not show any serum responses to the vaccines evaluated.

Subpopulations of B cells in PB were performed in the patients that were alive at the time of analysis (38/42). As shown in Table 2 and the Venn diagram A from Figure 1,

Table 2 Verification of updated ESID criteria in the CVID patients included in this study.

At least one of the following characteristics	
Increased susceptibility to infections (recurrent and/or opportunistic)	41/42 (97.6)*
Unexplained polyclonal lymphoproliferation (Hepato-splenomegaly)	1/42 (2.4)
Affected family member with antibody deficiency	10/39 (25.0)
AND marked decrease of IgG and IgA with or without low IgM levels (measured at least twice; <2 SD of the normal levels for their age)**	
IgG and IgA	42/42 (100)
IgG and IgA and IgM	29/41 (70.0)
AND at least one of the following	
Poor antibody response to vaccines	9/13 (69.2)
Low switched memory B cells (<70% of age-related normal values)	27/38 (71.0)
At least one altered test to evaluate B-cell responses	29/38 (76.3)
AND secondary causes of hypo-gammaglobulinemia have been excluded	
(e.g., infection, protein loss, medication, malignancy)	42/42 (100)
AND diagnosis is established after the 4th year of life (But symptoms may be present before)	42/42 (100)
AND no evidence of profound T-cell deficiency, defined as 2 out of the following:	
Decrease in the total number of T cells CD4+	
In patients 2–6 year-old (<300 cells/μL)	0/8 (0)
In patients 6–12 year-old (<250 cells/μL)	0/5 (0)
In patients >12 year-old (<200 cells/μL)	0/26 (0)
Decrease in the percentage of T cells CD4+ Naïve	
In patients 2–6 year-old (<25%)	0/8 (0)
In patients 6–16 year-old (<20%)	0/8 (0)
In patients >16 year-old (<10%)	0/12 (0)
Absent T-cell proliferation	0/9 (0)
No evidence of profound T-cell deficiency (with two criteria)	32/38 (84.2)

*Absolute numbers and percentages (in parenthesis) of patients that fulfilled the corresponding criterion.
**Serum immunoglobulin levels were evaluated only once in our census of patients.

Table 3 Responses to vaccination in the CVID patients.

Vaccine type	Non-responders	Responders	Total
Pneumo 23	2	2	4
Diphtheria toxoid	3	0	3
Hepatitis B	1	0	1
Rubella	3	0	3
*Both Rubella and Hepatitis B	0	2	2
Total	**9**	**4**	**13**

*These patients responded to Rubella but not to Hepatitis B and were therefore considered as responders.

27/38 (71%) exhibited memory B cell subpopulation percentages below the normal values to age. Of the 11 patients with normal memory B cell subpopulations, two were non-responders to vaccines (one unresponsive to the Pneumo®23 vaccine and another one to the diphtheria toxoid), also fulfilling the ESID criteria for CVID. In the remaining nine patients, we found other defects in the B cell compartment in PB, either altered (decreased or augmented) transitional or expanded $CD21^{low}$ B cells.

Exclusion of the secondary causes of hypogammaglobulinemia

ESID criteria recommend ruling out secondary causes of hypogammaglobulinemia. One patient from our census was documented as having taken steroids, one of the medications listed to cause hypogammaglobulinemia by ESID. However, the decrease in the Ig persisted after stopping the medication. Human immunodeficiency virus (HIV) infection was discarded in 14 patients. Bone marrow biopsy was documented in two patients, ruling out malignancies or lymphoproliferative diseases in blood cells. Moreover, all patients reported normal leukocyte blood counts and morphology. Sixteen of our patients reported protein electrophoresis analysis with normal albumin and decreased gamma fraction. In the other 15 patients, total serum protein quantification was among normal values.

Diagnostic age and evaluation of the T-cell-mediated immunity

Finally, ESID recommends making the definitive diagnosis of CVID only after the age of four and exclude T-cell lymphopenias (with at least two of the recommended tests) in patients that fulfill the previous criteria mentioned above. All patients in the present study were older than 4 years of age at diagnosis and all the Ig measurements and lymphocyte immunophenotyping were performed thereafter.

Subpopulations of T cells in PB were extracted from the analysis of the blood mononuclear cells (T, B, NK cells, and monocytes) found in the clinical records. We included an additional report of CD3+/CD4+/CD8+ T lymphocytes from a deceased patient. Importantly, none of the patients (0/39) had any evidence of CD4+ T-cell lymphopenia, according to the cell values established by ESID 2019.[9]

The previous data were complemented with the extended characterization of the CD4+ T-cell subpopulations (Naïve, effector, and central memory) in the reachable patients (28/38, 73.6%). None of them (28/28) exhibited decreased percentages of naïve CD4+ T cells according to the ESID 2019 criteria. We only found T cell proliferation reports to phytohemagglutinin (PHA) in the clinical records of nine patients and the responses were comparable to those in healthy controls. The two tests to evaluate T cell responses as required by ESID[9] were performed in 32/38 (84.2%) of our CVID census: five with normal total and naïve CD4+ T cell numbers and proliferation, four with normal total CD4+ T cell numbers and proliferation, and 23 with normal total and naïve CD4+ T cell numbers (See Venn diagram B in Figure 1).

Sources of the information

In an attempt to show evidence about the difficulties in the access to the most specialized test required for the diagnosis of CVID through the healthcare system, we also present a summary of the sources of the information to evaluate the registry working definition for CVID in our patients[9] (Table 4). Missing subpopulation tests were financially supported with the budget of the present and previous research grants in the reachable patients because they required these evaluations in the workflow.[20]

Clinical information and serum Ig levels were found in all the clinical records included. There were no reports of immunophenotyping of B cell subpopulations in the clinical records. However, 22/42 patients had previous PB B cell analysis financially supported with funds from another report[20] and we performed 16 in the present study (Table 4). Regarding the analysis of the naïve T cells, six of these reports were found in the clinical records and 22 were performed in the course of the present study. Analysis of T cell proliferation was found in the clinical records of nine patients.

In summary, our data showed that all the required immunological tests as considered by ESID[9] were performed in 32/38 (84.2%) patients. With regards to the

Table 4 Sources of information to evaluate lymphocyte subpopulations and response to vaccination.

Source of information	Clinical records	Previous studies	Present study	Total
Clinical information, age	42	0	0	42
Serum Ig at diagnosis	42	0	0	42
Responses to vaccination	13	0	0	13
B cell subsets	0	22	16	38
Total $CD4^+$ T cells	39	0	0	39
T cell subsets	6	0	22	28
T cell proliferation	9	0	0	9

humoral immunity evaluation, 29/38 patients (76.3%) presented and fulfilled all the registry working definitions for CVID.[9] The remaining nine patients exhibited other defects in the B cell compartment that have previously been considered among the B cell defects associated with CVID.[21,22] Vaccination responses, naïve T cell numbers, and T cell proliferation were the less documented parameters. Also, the evaluation of vaccination responses was very heterogeneous, including the measurement of serum antibodies to several different antigens, either proteins or polysaccharides.

Discussion

CVID is considered the most common symptomatic PAD disorder. The burden of the disease is considerably higher than the burden of other common conditions such as depressive disorders or diabetes mellitus, among others.[4] However, CVID is a heterogeneous immune syndrome, likely because environmental factors influence the underlying immunological defects in the affected patients, complicating the diagnosis. This syndrome is also considered a diagnosis of exclusion, which means that whenever the underlying cause of the immune defect is found, the patient is re-classified as belonging to the corresponding group. In the absence of a single clinical characteristic or laboratory test for the diagnosis of CVID, several reports suggest that a list of criteria is needed.[9,10] Other researchers have compared those criteria and added guidelines for their proper interpretation.[13,23,24] In our settings, the ESID registry working definition for CVID is a powerful tool to characterize the hipogammaglobulinemic patients.[9]

Most of the patients included here fulfilled the clinical criteria defined by ESID and also exhibited decreased serum IgG and IgA levels.[9] One of the major obstacles to studying the fulfilment of the current registry working definition for CVID in the present work was that all the patients included in our census were diagnosed before the year of publishing those criteria.[9] It is therefore difficult to keep the clinical records updated with all the required evaluations and tests. For example, only one Ig measurement and a minimum age of 2 years were necessary for the diagnosis before 2014. However, two serum Ig measurements and a minimum age of 4 years are required for the diagnosis according to the updated set of criteria in 2019.[9] Although all our patients were diagnosed after the age of four, they had only one serum Ig measurement pre-diagnosis. This was also problematic in other studies.[24] However, the international consensus for CVID diagnosis establishes that the repeated Ig measurement can be disregarded if either the IgG levels are below 100–300 mg/dL, depending on age, or if there are clinical considerations to start the Ig replacement as quickly as possible.[13] Currently, we performed the two required Ig measurements and a serum protein electrophoresis to confirm the hypogammaglobulinemia in the CVID suspicious patients who have no indication to speed up the replacement SCIG/IVIG therapy.

Most of the patients enrolled in the present study (29/38, 76.3%) fulfilled the ESID criteria related to the B-cell immunity evaluation. In our census, two patients had only poor responses to vaccines and 27 had decreased percentages of PB memory B cells. There is a discussion about which vaccines should be required for evaluation and the different vaccination response outcomes in CVID.[10] In New Zealand, vaccination with *Haemophilus influenzae* type B, Pneumovax® as well as diphtheria and tetanus toxoids are required in patients with IgG>3 g/L.[24] However, this aspect is not specified in the registry working definition for CVID.[9] The international consensus document for CVID recommends the evaluation of one T-cell dependent and one T-cell independent antigen.[13] In our census, the evaluation of vaccination responses to either T-cell independent (Neumo®23) or dependent antigens was only performed in four and nine out of 42 patients, respectively. The reason for this low number of patients with vaccination response studies is likely the availability of the vaccines at diagnosis, which most of the time is suboptimal. In our settings, Hepatitis B and Rubella are the most available vaccines, however, Neumo®23 has periods of shortage. Another controversial aspect in this regard is the heterogeneous response outcomes. In our census, among the studies with protein vaccines, again Hepatitis B and Rubella were the most easily available antigens to evaluate. Evaluation of diphtheria and tetanus toxoid vaccination responses is rarely available. This is without considering that diphtheria toxoid is a poor immunogen and also that only 5–10% of vaccinees are "non-responders" to Hepatitis B.[10,25] All these difficulties to implement and evaluating responses to vaccination during CVID diagnosis are likely the reasons why Ameratunga excluded these studies from the main categories of criteria to consider a probable case of CVID.[10,24] Whether these alternative diagnosis criteria are logistically more suitable in low-resource settings like ours needs to be evaluated.

Our results also showed that 71% of the CVID patients (27/38) included here exhibited a decrease in PB memory B cells. In a 30-year follow-up study, Baloh et al.[26] reported similar percentages of CVID patients (41/52 patients, 78%) fulfilling these criteria, however, the remaining patients exhibited other alterations in the B cell compartment. Since we found similar alterations in patients with normal memory B cells, other B cell abnormalities may be considered among the working definition for CVID, as defined by Ameratunga. They include the increased CD21 low subsets among the criteria to evaluate PB B cell subpopulations.[10] The heterogeneity in the B-cell abnormalities is also contemplated in the international consensus for CVID.[13] Moreover, alterations in PB transitional B cells or plasmablasts, which indicate pre- and post-germinal center defects, respectively, have been reported in association with some CVID phenotypes.[21,22]

In regard to the evaluation of the T cell compartment, no alterations in total CD4+, naïve CD4+ T cells, and T cell proliferation were demonstrated in 39, 28, and 9 of our patients, respectively. Overall, 32/38 (84.2%) of our patients were subjected to two of the recommended PB test to evaluate cellular immunity. These criteria are important to rule out combined immunodeficiencies. However, recent reports indicate that reductions of less than 10% in naïve T cells are not sensitive to discriminate between CVID and combined deficiencies.[27] Beyond the usefulness of the T-cell values included in the criteria,

T-cell characterization should be completed, even after the initiation of the SCIG/IVIG therapy, because they may inform us about prognosis. This is in accordance with the reports by Bateman et al,,[28] who demonstrated that some of these subpopulations are related to non-infectious comorbidities in CVID patients.

Finally, all the B- and T-cell subset evaluations in our patients were performed through funds from research grants.[20] This emphasizes the important role that research has in the study of rare diseases. However, it also raises concerns about the timely care of our patients by the Colombian health care system. Without the support of the third-party payers, only 34.2% of our patients would have completed the required evaluations. How do we classify the CVID patients with missing information for the diagnosis? A Danish CVID study suggested to label those patients as "inadequate investigation".[29] Under the ESID working definitions, they would fall under "unclassified immunodeficiencies".[9] This would put them in the same group with others with very different phenotypes. However, the clinical manifestations and type of hypogammaglobulinemia in our patients are still more compatible with CVID. This is still an unresolved question but, we should not forget that CVID diagnosis is always dynamic and might change according to the patient's information available, the course of the disease, and the genetic studies.[9]

Conclusions

Taken together, our results suggest that decision-making about the management of CVID patients is initially taken based on the clinical phenotype and the confirmed hypogammaglobulinemia, in most cases. Access to vaccines and evaluation of vaccination responses is limited. As an alternative, the B cell subpopulation could be evaluated, even after the initiation of the SCIG/IVIG therapy, but other B cell defects beyond the decreased switched-memory B cells in PB should be contemplated among the criteria. Even at follow-up, an analysis of T-cell numbers and function should be completed to rule out combined deficiencies and adjust management. Without the support of third-party payers, many of our patients would be labeled as "inadequate investigation" or "unclassified immunodeficiencies", but we do not know the impact of this classification on the appropriate management of these patients in our settings.

Acknowledgments

This work was supported by the Ministerio de Ciencia, Tecnología e Innovación from Colombia (Grant number 111-569-34426). Thank you to Michael Brims for the critical review of this manuscript.

Conflict of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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