Clinical and immunological assessment of 94 patients with primary humoral immunodeficiency: Common variable immunodeficiency, selective IgA deficiency and polysaccharide antibody deficiency syndrome

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Abstract. We present the clinical and B cell immunophenotypical characterization of 94 patients with Common Variable immunodeficiency (CVID), selective IgA deficiency (SIgAD) and polysaccharide antibody deficiency syndrome (SAD). Study design: We retrospectively investigated clinical findings and B cell compartment in 31 patients with CVID, 35 with SIgAD and 28 with SAD. Regardless of underlying disease, a delay was observed between age at diagnosis and onset of first symptoms. The predominant clinical findings were upper and lower respiratory tract infections. Allergic symptoms were more frequent in SAD and SIgAD patients, hematological and autoimmune manifestations in CVID and celiac disease in SIgAD. B-cell Immunophenotype abnormalities were observed in SAD and CVID patients: both had reduced memory B cells ($CD19^+$ $CD27^+$), and increased transitional B cells ($CD24^{++}$ $CD38^{++}$) was found in SAD. We did not find any statistically significant abnormalities in any of differentiation stages of B cells in SIgAD. Defects of the B cell compartment were associated with bronchiectasis, splenomegaly, autoimmunity and/or malignancy in CVID and SAD patients. We conclude that flow cytometric evaluation of the B cell compartment could be a useful tool for the diagnosis and follow up of these patients.

Keywords: Common variable immunodeficiency, IgA deficiency, polysaccharide antibody deficiency syndrome

1. Introduction

Primary immunodeficiencies (PID) are genetic diseases with heterogeneous clinical presentation. These disorders represent a challenge for clinical and basic immunologists, since in recent years they have paved the way for understanding several mechanisms of the innate and adaptive immunity. Currently there are more than 200 genetic abnormalities linked to PID diagnosis [1].

In 2006, the Latin American Group for PID reported 3321 cases of PID, from which 53% were of the humoral type, which also accounted for 73% of the PID cases in the last Argentinean Registry (performed in 2005). In both these series the most common deficiency was selective IgA deficiency (SIgAD) which affected 1/700 live births, and common variable immunodeficiency (CVID) which affected 1/25000 [1,2].

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Primary humoral immunodeficiency (PHID) patients may present with either recurrent or first invasive infections caused by common microorganisms. Several diseases, including autoimmune disorders, celiac disease, severe asthma, hematological disorders, etc., can be associated to PHID or can even constitute the only clinical manifestation. Most cases present in the early childhood, but some patients can manifest their first symptoms in the adolescence or in adulthood life.

The levels and specific antibody response of immunoglobulins can vary widely, from total absence or severe diminution (agammaglobulinemia), reduction of one or two isotypes (dysgammaglobulinemia or hypogammaglobulinemia), alterations in class switching, deficiency of only one isotype (SIgAD), altered response to challenge with polysaccharide and/or protein antigens [3–7].

The pathogenic mechanisms described include: 1) early defects in B lymphocyte (BL) development, 2) defects in class switching, 3) defects in the development of germinal centers, 4) impairment of T-B lymphocyte collaboration, or 5) defects in co-stimulatory molecule signaling pathways [6,8].

Despite being among the most frequent PID, the etiology of the molecular defects of polysaccharide antibody deficiency syndrome (SAD) and CVID remains poorly understood, and several research groups are trying to define the gene or genes involved. Four molecular anomalies linked to CVID have been identified in recent years (defects in ICOS, TACI, BAFF-R and CD19). These molecules are involved in the signals necessary for immunoglobulin class switching and for BL survival [8]. Abnormalities of the memory BL compartment have been described in patients with X-linked hyper IgM syndrome. This has led to assessment of BL in peripheral blood in other conditions with predominantly antibody defects [9–12].

BL originate in bone marrow from a common precursor or pluripotential stem cell. When these precursors differentiate, they rearrange and express their receptor on the surface, and migrate to peripheral blood as transitional BL (tBL). In man, these early emigrants are characterized phenotypically by a high expression of CD38 and CD24. This tBL population constitutes a very small fraction of functionally immature cells that circulate in the peripheral blood of adults. The naïve BL that originate from tBL can respond to an antigenic stimulus in secondary lymphoid organs, proliferate and differentiate into memory B cells and antibody-producing plasma cells. In normal individuals, memory B cells represent 40% of the total BL in peripheral blood, and are characterized by the surface expression of CD27. According to the surface expression of immunoglobulin, these cells can be further divided into switched memory BL (CD27$^+$ IgM$^-$ IgD$^-$) and non-switched memory BL (CD27$^+$ IgM$^+$IgD$^+$). IgM memory BL can be detected in the absence of germinal centers, require the spleen for their generation, function and are involved in T-independent response [3,12–14].

Recently, independent groups have published on the association between BL compartment and the various clinical manifestations in CVID patients [10,11]. Alachkar et al. [15], in a cohort of 55 patients with CVID and SAD, found an association between reduced switched memory B cells and the incidence of bronchiectasis and splenomegaly. However, the median switched memory B cell percentage of the SAD did not differ from that of a control group [15]. Here we present the clinical findings and BL immunophenotypic characterization of 93 patients with CVID (31), SIgAD (35) and SAD (28) managed in our Unit.

2. Materials and methods

2.1. Patients and healthy donors

We performed a retrospective study of a cohort of 31 patients with CVID, 35 with SIgAD, 28 with SAD, diagnosed between 1997–2008.

2.1.1. CVID
CVID was classified according to European Society for Immunodeficiency diagnostic criteria (www.ESID.org) [16]. Patients older than 2 yr who had a marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA were considered to have probable CVID. Patients older than 2 yr who had a marked decrease (at least 2 SD below the mean for age) in one of the major isotypes (IgM, IgG and IgA) were deemed to have possible CVID.

2.1.2. SIgAD
SIgAD was diagnosed in patients older than 4 yr with two serum IgA measurements equal or lower than 7 mg/dL, according to the ESID diagnostic criteria (www.ESID.org).

2.1.3. SAD
SAD was diagnosed in patients unresponsive to challenge with the 23-valent pneumococcal vaccine, and normal or near-normal serum levels of immunoglobulins.

2.1.4. Healthy controls

30 age-matched healthy donors (HD) were included. As levels of B cells subsets are age dependent parameters, we divided them into three groups: less than 4 yr old, 4 to 11 yr old, and over 11 yr of age. We excluded patients with hypogammaglobulinemia but confirmed diagnosis of other PHID (agammaglobulinemia, hyper-IgM syndrome, X-linked lymphoproliferative disease, transitory hypogammaglobulinemia, hypogammaglobulinemia secondary to neoplasms or anticonvulsive treatment).

2.2. Measurements of specific antibodies

Serum antibodies concentration to 7 pneumococcal serotypes (1, 3, 5, 6b, 7, 14, 23 F) were measured by a 3rd generation enzyme-linked immunosorbent assay [17] 40 days after immunization with Pneumo 23 vaccine (Aventis Pasteur). Impaired response to polysaccharide antigens was arbitrarily defined as titers fewer than 1,3 ug/mL in at least 4 of the 7 serotypes evaluated post immunization Isohemagglutinin titers were measured by standard methodology. Enzyme linked immunosorbent assays were used to measure the antibody level to tetanus toxoid (TT) and viral antigens. An adequate TT response was considered at titers greater than 0.1 UI/mL.

The following data was collected from medical records retrospectively: number and type of infection, and presence of bronchiectasis, splenomegaly, autoimmunity, and celiac disease. We could not obtain bacterial cultures for typing from all the patients. The time periods between the first appearance of symptoms suggestive of PID and referral to the Immunology unit were recorded.

Once the diagnosis was established, all the CVID patients and 27 patients with SAD began to receive intravenous immunoglobulin replacement therapy every 21 to 30 days. Replacement therapy was well tolerated by 96.5% of the patients. The rate of hospitalizations for acute and severe complications was reduced by 80% since replacement therapy initiation. One patient with CVID died, due to lymphoma.

2.3. Immunophenotyping of B lymphocyte

Whole EDTA blood samples (300 μl) were washed 4 times with PBS and the cells were labeled with the following antibody panel: CD5 FITC (BD)/CD21 PE (BD-Pharmingen)/CD20 PerCP-Cy5-5(BD)/CD38 APC (BD); IgM FITC (BD-Pharmingen)/CD27 PE-BD/CD19 PerCP-Cy5-5 (BD)/CD38 APC (BD); IgD FITC (BD-Pharmingen)/CD27 PE-BD/CD19 PerCP-Cy5-5 (BD)/CD38 APC (BD); IgD FITC (BD-Pharmingen)/CD24 PE-BD/CD19 PerCP-Cy5-5 (BD)/CD38 APC (BD). Cells were analyzed by flow cytometry (FACScalibur Becton Dickinson) and 5000 CD19 $^+$ events were selectively acquired using Cell Quest software. B cell populations were analyzed as follows: memory (mBL, CD27$^+$), naive (CD27$^-$IgD$^+$ IgM$^+$), non-switched memory (CD27$^+$ IgD$^+$ IgM$^+$), switched memory (CD27$^+$ IgD$^-$ IgM$^-$), and tBL (CD24^{++} CD38^{++}).

All patients and their relatives were informed about the clinical study and provided written informed consent.

2.4. Statistical analysis

The demographic characteristics, clinical features and B cell compartment were summarized using median and range, mean $\pm$ SD for continues variables and number (percentage) for categorical variables.Differences among patient groups and HD were evaluated using Kruskall Wallis ANOVA, followed by the Dunnet's multiple comparison tests. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Demographic data of the studied groups (Table 1)

3.1.1. CVID group

Patients' ages were heterogeneous, encompassing 10 adult and 21 pediatric patients. The median ages of onset of symptoms were 4 (range 1–16) yr for the pediatric group and 32.5 (range 18–60) yr for the adult group. The median ages at diagnosis were 8.5 (range 3–17) yr and 41.0 (range 18–69) yr, respectively. The mean delays in diagnosis were therefore 4.5 yr and 9.5 yr respectively. 64% of the patients were female. None had a history of consanguinity or a family history of PID, but some had family history of hypothyroidism, malignancy and autoimmunity. According to the ESID criteria, the CVID diagnosis was possible in 39% of patients and probable in 61%. Polysaccharide antigen response was measured in every CVID patient, and was negative in all of them. 9 of 19 patients evaluated had normal antibody levels to TT; the response to viral antigens was normal in 8 and low in 20 patients.

Table 1
Demographics and clinical characteristics of CVID, SAD and SIgAD patients

	SIgAD (n: 35)	CVID (n: 31)	SAD (n: 27)
Gender			
Female/male	21/14	20/12	10/17
Age at diagnosis (years) Children/adults median (range)	12 (5.8–18)	8.5 (3–17)/41(18–69)	7 (2–14)
Age at first symptoms (years) Children/adults median (range)	2 (0.25–9)	4 (1–16)/32.5 (18–60)	1.5 (0.1–6)
ESID criteria		Possible:12 Probable:19	
Clinical findings			
Infections	26 (74%)	30 (97%)	26 (93%)
Acute otitis media	14 (40%)	16 (52%)	10 (36%)
Sinusitis	10 (29%)	19 (61%)	6 (21%)
Pneumonia	17 (48%)	29 (93%)	24 (86%)
Bronchiectasis	1 (2%)	19 (61%)	13 (43%)
Diarrheas	7 (20%)	6 (19%)	0
Recurrent parotitis	0	5 (16%)	0
Autoimmunity	9 (26%)	7 (23%)	0
Cytopenia	2 (6%)	5 (16%)	0
Celiac disease	6 (17%)	0	0
Atopy	24 (69%)	14 (45%)	15 (54%)
Splenomegaly	7 (29%)	8 (26%)	0
Granuloma	0	1 (0.3%)	0
Malignancy	0	4 (13%)	0

CVID: Common variable immunodeficiency, SIgAD: Selective IgA deficiency, SAD: Polysaccharide antibody deficiency syndrome.

The predominant clinical presentations were upper and lower respiratory tract infections. Pneumonia was found in 93% of the patients, acute otitis media in 52%, and chronic sinusitis in 61%. In our series, only one female patient presented with meningitis and sepsis. Atopic signs (rhinitis, allergic conjunctivitis and asthma) were found in 45% of the patients. 23% of CVID patients had at least one autoimmune disease: idiopathic thrombocytopenic purpura (ITP) in 3, neutropenia in 2, Sjogren syndrome in 1 and vitiligo in 1.Recurrent parotitis was found with a relatively high frequency (16%). 61% of the patients presented bronchiectasis. In our series, malabsorption syndromes were less frequent than observed in other reports, 19% of the patients presenting with recurrent diarrhea. Splenomegaly was present in 26% of the patients. A lesion compatible with a lung granuloma was detected by Chest Computerized Tomography scan in only one patient [18].

CVID constituted the only group with associated malignancy, and which included the death of a patient due to lymphoma during the study. Four patients with a history of recurrent infections also presented with hematological disease (benign monoclonal gammapathy, Hodgkin's lymphoma, and EBV Burkitt lymphoma).

3.1.2. SIgAD group

A total of 35 patients (14 male, 21 female) were included, all of which were symptomatic. Median age at diagnosis was 12 yr. In all children symptoms onset was before 4 yr, and the diagnosis was established 3 to 4 yr after first consultation.

Respiratory infections were the most frequent manifestations (74%): pneumonia (48%), ear infection (40%), sinus infection (29%). Atopic symptoms (allergic rhinitis, eczema, asthma) were found in 69% of the patients. Autoimmune disease constituted the first manifestation in 26% of the patients: type I diabetes in 2, hyperthyroidism or Graves disease in 1, early puberty in 1, idiopathic thrombocytopenic purpura in 2, rheumatoid arthritis in 2, recurrent autoimmune parotitis in 1. Associated celiac disease was present in 17%, being the first manifestation in 3 patients.

During family screening for potentially affected relatives, SIgAD was found in 4 family members that had been asymptomatic.

3.1.3. SAD group

28 patients (18 males and 10 females) were unresponsive to polysaccharide antigens with normal immunoglobulins levels. Nineteen patients had normal antibody levels to TT and 4 had low levels. Isohemagglutinin measurement was normal in 16, and negative in 2, patients. Six patients had IgM levels more than 1 SD below normal values: these patients had normal isohemagglutinins. Only one patient had low IgG_2 and IgG_4 level. Symptoms onset was before 2 yr of age in 53.4% of the patients. All patients had history of recurrent and severe infections that required hospitalization. One patient who associated SIgAD was excluded from the study.

Table 2
B lymphocyte subsets in SIgAD, CVID, SAD patients and healthy controls for different age groups. Values are expressed as percentage of total B cells (mean ± SD)

	CVID n: 31	SIgAD n: 35	SAD n: 27	Controls n: 30	CVID vs. Controls P	SIgAD vs. Controls P	SAD vs. Controls P
CD27							
< 4 y	12,67 ± 5,80		14,04 ± 5,44	18,26 ± 6,3	> 0,05		> 0,05
4–11 y	13,49 ± 9,42	23.23 ± 7.92	11,20 ± 5,29	25,12 ± 7,1	< 0,001	> 0,05	< 0,01
> 11 y	17,45 ± 6,58	26.00 ± 1.11	11,06 ± 7,30	33,15 ± 7,1	< 0,001	> 0,05	< 0,001
$CD27^+gD^+gM^+$							
< 4 y	6,06 ± 2,67		5,79 ± 1,57	8,68 ± 3,23	> 0,05		> 0,05
4–11 y	8,30 ± 4,60	11.09 ± 4.49	8,32 ± 6,10	13,89 ± 3,89	> 0,05	> 0,05	> 0,05
> 11 y	12,49 ± 9,90	12.57 ± 5.66	4,07 ± 1,30	15,60 ± 4,87	> 0,05	> 0,05	< 0,01
$CD27^+IgD^-IgM$-							
< 4 y	6,61 ± 4,30		8,25 ± 4,22	9,58 ± 3,16	> 0,05		> 0,05
4–11 y	5,49 ± 5,08	11.96 ± 4.59	7,10 ± 4,01	11,62 ± 5,72	> 0,05	> 0,05	> 0,05
> 11 y	5,86 ± 8,20	13.64 ± 6.91	6,91 ± 6,22	17,55 ± 3,30	< 0,01	> 0,05	< 0,01
$CD24^{+++}CD38^{+++}$							
< 4 y	15,94 ± 5,41		23,07 ± 2,37	13,10 ± 4,45	> 0,05		> 0,05
4–11 y	12,07 ± 6,18	7.06 ± 2.4	21,10 ± 8,30	7,06 ± 1,78	> 0,05	> 0,05	< 0,05
> 11 y	7,80 ± 12,65	5.61 ± 5.21	24,48 ± 4,92	3,24 ± 0,81	> 0,05	> 0,05	< 0,001

CVID: Common variable immunodeficiency, SIgAD: Selective IgA deficiency, SAD: Polysaccharide antibody deficiency syndrome.

The most frequent clinical presentation was recurrent bacterial infections of lung and ear, while meningitis and sepsis were less common. Serotyping of pneumococcus strains was not performed in all patients. 43% of the patients had bronchiectasis confirmed by chest CT scan. Allergic manifestations were also common, especially in skin and respiratory tract.

3.2. Assessment of the B cell compartment in CVID, SAD and SIgAD (Table 2)

Relative and absolute values of BL were within normal limits in 91 patients. Two CVID female patients had values < 2% both with leukopenia (not shown).

3.2.1. CVID group
19 of 31 patients (60%) exhibited a reduction of mBL. Statistically significant reduction of mBL was found in 4 to 11 yr group (13.49 ± 9.42 vs. 25.12 ± 7.1, $P < 0.001$) and in older children (17.45 ± 16.58 vs. 33.15 ± 7.1, $P < 0.001$) compared with age-matched HD; mostly because of decrease of switched mBL. Transitional B cells were increased only in 6 patients.

3.2.2. SIgAD group
These patients were less likely to have impairment of the B cell compartment: only two patients had mBL reduction and tBL increase.

3.2.3. SAD group
57% of the patients exhibited a reduction of mBL and 67% had increased numbers of tBL. Both alterations were statistically significant in the 4 to 11 yr group

(mBL: 11.98 ± 5.79 vs. HD 25.12 ± 7.1, $P < 0.01$, tBL 21.50 ± 18.82 vs. HD 7.06 ± 1.78, $P < 0.05$), and in patients older than 11 yr (mBL, 11.06 ± 7.30 vs. 33.15 ± 7.1, $P < 0.001$, and tBL 24.48 ± 4.92 vs. 3.24 ± 0.81, $P < 0.001$).

3.3. Association of clinical parameters

The association between common clinical characteristics (bronchiectasis, splenomegaly autoimmunity and malignancy) and BL compartment defects (reduction of mBL and/or increase of tBL) are shown in Table 3.

3.3.1. CVID group
74% of the patients with bronchiectasis, 87% with manifestations of autoimmune disorders (cytopenia, vitiligo, Sjogren syndrome), 75% with splenomegaly (diagnosed by physical examination and abdominal ultrasonography) and 78% with malignant hematological diseases exhibited decrease mBL number. Five of seven patients with autoimmunity were classified as SmB^- and two as SmB^+ according to the classification scheme EUROclass trial [11].

3.3.2. SIgAD group
Two patients who had impairment of the BL compartment had associated recurrent infections and autoimmunity disease.

3.3.3. SAD group
73% of the patients with bronchiectasis showed alterations of the BL compartment, mainly an increase in tBL number. Nine of these patients had more than 9% tBL, but this was not associated with lymphoproliferation as described in CVID.

Table 3
Correlation of clinical characteristics and B cell compartment defects* in CVID, SIgAD and SAD patients

	CVID (n: 31)	SIgAD (n:35)	SAD (n:27)
Clinical characteristic/B cell compartment defect (BLD)			
Number of patients with bronchiectasis (BE)	19	0	11
Number of patients with BE and BLD (%)	14/19 (74%)	–	8/11 (73%)
Number of patients with Autoimmunity (AI)	8	15	0
Number of patients with AI and BLD (%)	7/8 (87%)	3/15(20%)[1]	–
Number of patients with splenomegaly (EM)	8	0	0
Number of patients with EM and BLD (%)	7/8 (78%)	–	–
Number of patients with malignancies (M)	4	0	0
Number of patients with M and BLD (%)	3/4 (75%)	–	–

*Reduced mBL and/or increased tBL compared with age-matched HD;
[1] Among patients with SIgAD and autoimmunity, 12 had celiac disease.

4. Discussion

Humoral deficiencies were the most frequent diagnosis in the group of patients seen in our hospital for recurrent respiratory infections. A diagnostic delay was observed in most patients, which may explain the recurrence of respiratory infections and progression to bronchiectasis. In agreement with previous reports, the CVID group was the most heterogeneous with regard to age of consultation and clinical presentation [11]. SAD patients had infections, especially recurrent sinusitis, bronchitis and pneumonia, that led to earlier consultation with the immunologist. The incidence of allergy symptoms was more frequent in SAD and SIgAD patients, while hematological and autoimmune manifestations were more common in CVID, and celiac disease in SIgAD.

An altered BL compartment was found in 60% of CVID patients, with a statistically significant diminution of mBL, especially switched mBL, which became progressive with age. These data agree with others reported in the literature, which reveal a failure of development pathways in germinal centers, resulting in an impairment of B cells to produce antibody-secreting cells.

The reduced levels of this population in peripheral blood is a manifestation of the unbalanced homeostasis of BL compartment in these patients. Some authors have related the serum immunoglobulin levels of CVID patients with the diminution of switched mBL [10]. In the present study, no correlation was found between BL defects and serum immunoglobulin levels. The defects of the mBL compartment were related to the most severe clinical manifestations such as autoimmunity, splenomegaly, malignancy, and bronchiectasis [6]. Approximately 23% of CVID patients presented autoimmune disease, similar proportion has been documented for other groups [19]. Several unresolved questions remain regarding the pathogenesis of autoimmunity in

CVID, but there has been speculation that the presence of immature cells unable to undergo immunoglobulin switch and somatic hypermutation has an important role in the retention of auto-reactive B cell clones [20].

Defects in the germinal centers reactions have been described in patients with mutations in the CD40L gene and the inducible co-stimulator molecule (ICOS). ICOS expression was studied in 15 patients with CVID and 10 patients with SIgAD and only three CVID patients had a diminished ICOS expression (data not shown) Two of these patients had a marked reduction of mBL, and one of them had associated autoimmunity. Since ICOS expression was reduced, it would be necessary to search for this molecular defect in both patients. Other anomalies, such as the increase of transitional BL, were not consistently found in CVID patients.

In the last 19 yr we have diagnosed 213 SIgAD cases. Recurrent bacterial infections and atopic episodes were the most frequent reasons for consultation. Autoimmune disorders and celiac disease were present in 20–25% of SIgAD patients. HLA class II molecules were investigated in 60 SIgAD patients and their relatives; 20 patients with celiac disease shared the HLA DR3 A17 antigen (data not shown).

The levels of mBL were comparable with the age-matched HD. Only in two SIgAD patients we found B cell alterations (mBL diminution and tBL increase) since early age, which required further observation as to whether they may develop CVID.

The SAD group was homogeneous in terms of clinical features. All presented recurrent and severe bacterial infections involving more than one organ, and the vast majority had also a history of respiratory and skin allergies. These data agree with those reported in the literature [4,5].

When B cell homeostasis of SAD patients was compared to CVID patients, both presented with diminution of mBL, but a greater transitional BL increase was found in the first group. Kruetzaman et al. reported a

diminution of IgM$^+$ mBL associated to a higher susceptibility to Streptococcus pneumoniae infections and bronchiectasis [3]. During the last yr it has been reported that, after LPS engagement, the TLR4 pathway requires the Bruton tyrosine kinase (Btk) to phosphorilate the p65 dimer that forms the NFkB heterodimer. Btk mutations produce a very early maturation arrest in B cell differentiation, whose characteristic clinical expression is X-linked agammaglobulinemia [18,21,22]. Btk dependent activation of NFkB is essential for reprogramming expression of genes that control B cell survival and proliferation [23]. Btk and other cytoplasmic protein tyrosine kinase defects may explain the alteration in the Btk-depent B cell receptor signaling.

Classification based on phenotyping of BL has become part of the standard diagnosis of patients with CVID. B cells subset quantification identifies patients with defects of germinal center dependent mBL formation and early defects of peripheral B cell differentiation. In addition, flow cytometric findings could help us to search genetic defects such as TACI, ICOS, BAFFR, CD19 mutations [24].

We also propose the evaluation of B cell compartment in other PHID patients for instance SAD and SIgAD. SIgAD is considered to be genetically linked with CVID, as the latter may develop from SIgAD. The persistence over the time of low levels of mBL may predict the development of CVID.

The diagnosis and treatment of SAD remains controversial and in the same way low levels of response to protein antigens have been described in some of these patients [25,26]. The BL compartment may be of clinically relevant and help to define groups with different prognosis as in patients with CVID. Future studies will improve understanding of the pathogenesis and define the utility of predictive markers in these PHID.

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