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ORIGINAL ARTICLE

Specific antibody deficiency and other antibody deficiencies in pediatric patients with recurrent infections

Deficiencia de anticuerpos específicos y otras deficiencias de anticuerpos en pacientes pediátricos con infecciones recurrentes

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What do we know about the subject matter of this study?

Antibody deficiencies, including specific antibody deficiency, represent the most frequent inborn errors of immunity. It is very important to suspect them and to include the study of the anti-pneumococcal response in the evaluation of pediatric patients with recurrent infections, mainly respiratory, in order to diagnose and treat them on time.

What does this study contribute to what is already known?

For the first time in Paraguay, we addressed the deficiency of specific antibodies, evaluating the anti-pneumococcal response by a global ELISA, which, with its limitations, is widely used in clinical laboratories. Thus, we provided the first data and implemented the diagnostic technique locally. We also found other antibody deficiencies and observed that the cut-off points for a post-PPV23 response, reported mainly for adults, would be useful in the pediatric population until a more accessible method to evaluate the anti-serotype response is available.

Abstract

Specific antibody deficiency (SAD) is characterized by a poor response to polysaccharide antigens and post-PPV23 anti-pneumococcal antibodies must be evaluated for its diagnosis. When this study was proposed, the diagnostic method for SAD was not available in Paraguay and there is no data on this deficiency in our country. **Objective:** To evaluate the presence of SAD and other antibody deficiencies by studying the anti-pneumococcal response and serum immunoglobulins in pediatric patients with recurrent infections. **Patients and Method:** 50 patients aged 2 to 17 years were included, who attended pediatric services at two public hospitals in Paraguay, between 2019 and 2022. Pre- and

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post-PPV23 serum anti-pneumococcal antibodies were measured by a global ELISA assay, as well as serum immunoglobulins IgA, IgG, and IgM by radial immunodiffusion, and IgG subclasses by automated method. **Results:** The median age was 5 years (IQR: 3-8), with a slight predominance of males (52.0%). Upper (70.0%) and lower (62.0%) respiratory infections and allergies (76.0%) were frequent. Anti-pneumococcal antibodies increased significantly ($p < 0.001$) post-PPV23, however, two patients (4.0%) presented poor anti-pneumococcal response and were defined as SAD cases. In addition, 5 isolated IgG deficiencies, 2 IgA deficiencies (DIgA), 2 DIgA-associated subclass deficiencies, and a common variable immunodeficiency were detected. **Conclusions:** We provide the first data on the specific antibody deficiency and implement the diagnostic technique in our country. It is necessary to continue strengthening knowledge about these pathologies among local pediatricians to improve clinical suspicion, diagnosis, and treatment.

Introduction

Primary immunodeficiencies (PIDs) are rare, chronic, and severe congenital disorders of the immune system. Affected patients cannot develop an adequate immune response, leading to severe and recurrent infections (RI), autoimmunity, autoinflammation, and allergies[1]. They are currently referred to as inborn errors of immunity (IEI), with 485 associated genetic disorders. About 50% are predominantly antibody deficiencies (PADs), which are caused by defects in the development and/or function of B lymphocytes[2].

PADs are classified as: common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), hyper-immunoglobulin (HIgM) syndrome, IgA deficiency (IgAD), IgG subclass deficiencies, and specific antibody deficiency (SAD), among others. The first four presented decreased levels of IgA, IgG, and/or IgM, unlike SAD, where these immunoglobulins are normal but the response to polysaccharides antigens is deficient[2,3].

SAD presents with a deficient response to *Streptococcus pneumoniae* (pneumococcus) polysaccharides, and its molecular defect is still unknown. It is characterized by RI such as sinusitis, otitis, and pneumonia[4] and there may be a lack of response to treatment in allergic children[5]. For its diagnosis, it is necessary to evaluate the serological response to non-conjugated pneumococcal vaccines, determining antibody titers in response to PPV23[1,6]. Its prevalence is not known exactly; some studies report 5%-10% in children with recurrent respiratory infections[7].

In Paraguay, IEIs diagnosed are registered at the Instituto de Medicina Tropical/Centro Nacional de Inmunodeficiencia Primaria (IMT-MSPyBS) and reported to the Latin American Society of Immunodeficiencies (LASID). To date, there are 33 cases[8], which would indicate an underdiagnosis and/or underreporting at the local level. Besides, the Instituto de Investigaciones en Ciencias de la Salud (IICS-UNA) is the only center in the country that offers laboratory tests for IEI detection; however, at the time of this study, we did not have the method to detect SAD and we lacked local information on this deficiency. The objective of this study was to evaluate the presence of SAD and other antibody deficiencies by studying the anti-pneumococcal response and serum immunoglobulins in pediatric patients with RI in public hospitals, in order to implement the diagnostic technique for SAD and provide the first data in Paraguay.

Patients and Method

Descriptive, observational, longitudinal study with sample collection performed pre- and post-PPV23 vaccination to quantify anti-pneumococcal antibodies. This procedure (diagnostic vaccination) followed international protocols already established for the diagnosis of SAD[7,9].

Study population and characterization

We included 50 patients aged 2 to 17 years, with RI and treated in pediatric infectious diseases services of two public hospitals (IMT-MSPyBS and HCL-FCM-UNA), from May 2019 to November 2022. Patients presented at least one of the following clinical signs (10): ≥ 2 pneumonia episodes in one year, ≥ 3 otitis in one year, ≥ 2 sinusitis in one year, recurrent abscesses in skin and/or organs, and ≥ 1 deep/severe infection (sepsis, meningitis). Patients with established diagnosis of IEI or secondary immunodeficiency, hemato-oncological pathology, and those who did not complete vaccination were excluded. Clinical-demographic characteristics were evaluated such as age, sex, origin, educational status, RI ≥ 2 times per year (upper and lower respiratory tract, otitis, sinusitis, adenopathies, skin infection, others), and severe infection on at least one occasion (severe pneumonia, sepsis, abscesses, meningitis), age at the onset of infections, number of infections per year, hospitalizations per year, admission to intensive care unit, allergy and/or autoimmunity. In addition, we ask about family history related to IEI, such as early unexplained infant death, and siblings with RI, among others. Regarding the PCV vaccination schedule (before the study), the number of doses and time since the last dose were considered.

PPV23 immunization and blood samples

Once the guardian of the minor agreed to participate, the physician identified the patient and performed a clinical evaluation, indicating vaccination with PPV23 (Pneumo23). The patient was referred to the research center (IICS-UNA), where the pre-PPV23 blood sample was collected. The patient was then referred to the IMT-MSPyBS vaccinator service to receive PPV23. The patient attended the IICS four weeks later for the second sample collection (post-PPV23). Three mL of venous blood was drawn (pre- and post-PPV23), following safe protocols and by trained personnel.

Anti-pneumococcal antibodies and definition of poor response

Serum anti-pneumococcal IgG concentration (mg/L) was determined by global ELISA (VaccZyme™ Anti-PCP IgG kit, Binding Site Group Ltd., Birmingham, UK) with an antigenic pool of 23 pneumococcal serotypes. Serum antibody levels were determined in pre- and post-PPV23 samples, following the kit manufacturer's instructions. The absorbances were measured using an ELISA reader (HumaReader Single, Human, Germany).

Poor anti-pneumococcal response was considered when post-PPV23 antibody levels were ≤ 110 mg/L[11]. For pre-PPV23 levels > 110 mg/L, a post/pre-PPV23 increase less than 2 (two) was considered poor response[9,12]. Pre-PPV23 samples > 110 mg/L and post-PPV23 samples ≤ 110 mg/L were evaluated in a second run for value verification.

Anti-pneumococcal response according to age and previous PCV vaccination

The population was stratified according to age, previous PCV doses, and time since the last dose. Age groups were divided as follows: 2-3 years (n = 14), 4-5 years (n = 13), 6-8 years (n = 11), and > 8 years (n = 12). Patients were grouped according to previous PCV doses as: no dose (n = 11), 2 doses (n = 5), and ≥ 3 doses (n = 34) and according to the time elapsed in months (n = 39) as: < 36 (n = 15), between 36 and 60 (n=12), >60 (n=12). Antibody levels, pre- and post-PPV23, were compared between the different groups.

Total serum immunoglobulin levels and subclasses of IgG

The serum concentration (mg/dL) of IgA, IgG, and IgM was determined through the radial immunodiffusion (RID) method, using commercial plates (Diffu-Plate, Biocientífica S.A., Buenos Aires, Argentina), in the pre-PPV23 samples. According to age, the interval values established by the manufacturer of the plates were used as a reference, considering hypogammaglobulinemia when the value was lower than the reference. Each sample that presented decreased IgA, IgG, and/or IgM values was reevaluated to verify the result.

IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were measured by the automated turbidimetric method (SPAPlus®, Binding Site Group Ltd., Birmingham, UK). The calibrators and controls kits were used as well as the manufacturer's reference values, according to age.

Specific antibody deficiency (SAD) and other antibody deficiencies

The presence of SAD was established in patients with poor anti-pneumococcal response (post-PPV23 ≤ 110 mg/L, or post/pre-PPV23 < 2), with normal levels of IgA, IgG, IgM, and IgG subclasses[1-3]. Other antibody deficiencies such as CVID, IgAD, IgG subclass deficiency (IgGSD), and isolated IgG deficiency (IgGD), were defined according to diagnostic criteria of the American Academy of Allergy, Asthma, and Immunology (AAAAI)[1] and the phenotypic diagnostic algorithms of the International Union of Immunological Societies (IUIS)[2,3].

Ethical considerations

Informed consent was obtained from each patient. All procedures were free of charge and laboratory results were provided within six weeks. Immunization with PPV23 was for diagnostic purposes and provided the patient with additional protection against pneumococcus. International criteria for antibody deficiencies were used; however, the final diagnosis and treatment were performed by a physician specializing in PIDs (IMT-MSPyBS). The working protocol was approved by the IICS-UNA Research Ethics Committee (P08/2019).

Statistical analysis

The data were analyzed with the SPSS statistical software (IBM Corp.). Absolute frequencies (n) and percentages (%) were used for categorical variables. The Kolmogorov-Smirnov test was applied to quantitative variables, using medians and ranges due to the asymmetric distribution. Pre- and post-PPV23 antibody levels were compared using the nonparametric Wilcoxon test for related samples. To compare antibody levels (pre- and post-PPV23) according to age and previous PCV status, the Kruskal-Wallis nonparametric test was used ($p < 0.05$).

Results

Clinical-demographic characterization of patients

Fifty patients with RI were evaluated. The median age was 5 years (IQR = 3-8), 52.0% were male, and most of them resided in cities of the Central Department of the country. 64.0% (32/50) of the patients were of school age, and 40.6% (13/32) of them had frequent school absences due to RI. Infections (≥ 2 episodes/year) of the upper and lower respiratory tract predominated. Allergies were observed in most patients, mainly asthma (26.0%) and allergic rhinitis (30.0%). Table 1 shows the clinical-demographic characterization of patients. Other clinical characteristics evaluated were age at the onset of infections (in years), number of infections per year, number of hospitalizations (last year), and days of hospitalization, with the following medians respectively: 2 (IQR: 1-5), 3 (IQR: 2-5), 1 (IQR: 1-2), 7 (IQR: 5-14).

Anti-pneumococcal antibodies pre- and post-PPV23

We observed a median of 46.8 mg/L for pre-PPV23 serum antibodies (Table 2). Levels ranging from 2.3 to 26.9 mg/L (reported protective level < 27.5)[13] were observed in 17/50 patients, 12 of them having three doses of PCV, 2 patients having two doses, and only three (≥ 10 years of age) having no PCV. Very low values (2.3 to 9.4 mg/L) were observed in 4 patients (2, 4, 8, and 17 years old), only the 17-year-old patient did not have PCV. On the other hand, pre-PPV23 levels of 125.4 to 168.7 mg/L (> 110) were observed in 4/50 patients. These patients were 8, 9, 13, and 16 years old, and only the first two had PCV.

In post-PPV23 antibodies, the median was 298.1 mg/L and the post/pre increase ranged from 1.5 to 77.1 (Table 2). 47 out of 50 patients responded adequately to PPV23 (> 110), or with post/pre increase > 2 (for pre-PPV23 levels > 110). This satisfactory post-PPV23 response is evident when comparing pre- and post-vaccine antibodies (Figure 1). However, a poor response was observed in 3/50 patients. In 2 of these patients (female, aged 7 and 17 years) values < 110 mg/L were observed (37.7 and 53.5 mg/L, respectively). In the third patient (male, 13 years old), with a pre-PPV23 level of 160.4 mg/L (> 110), a post-PPV23 level of 247.1 mg/L was observed, but the increase post/pre was 1.5 (< 2).

Total serum immunoglobulins and IgG subclasses

In addition to evaluating the anti-pneumococcal response, levels of IgA, IgG, IgM, IgE, and the four IgG subclasses were measured. These measures were performed to look for other antibody deficiencies. Table 2 shows the central and dispersion trend for these immunoglobulins. 80% (40/50) presented normal IgA, IgG, and IgM, however, in the total range for IgA and IgG we observed decreased values, thus, 20% (10/50) had hypogammaglobulinemia. On the other hand, 8% (4/50) had at least one decreased IgG subclass. These cases were defined as antibody deficiencies and are described below. As for serum IgE, 64% (32/50) had elevated levels, which would indicate a very likely allergic state.

Anti-pneumococcal response according to age and PCV schedule

Pre-PPV23 antibodies increased slightly with age (Figure 2, A). The medians (IQR) according to age groups were: 29.8 mg/L (20.9-44.3); 49.3 mg/L (17.5-57.6); 54.2 mg/L (27.8-78.6), and 66.0 mg/L (30.6-106.8). Regarding post-PPV23 levels, an increasing trend was observed up to 6-8 years and then a decrease in > 8 years (Figure 2, B), thus, the medians (IQR) according to age groups were: 276.4 mg/L (252.9-351.7); 315.1 mg/L (258.6-340.9); 367.9 mg/L (224.8-452.6), and 281.4 mg/L (183.6-375.4). The differences observed were not statistically significant ($p > 0.05$).

Regarding the PCV schedule, 11 patients had not received a dose. These patients were ≥ 10 years old and their schedules did not include it (in 2012 PCV was introduced in Paraguay). In 2/50 patients, 4 doses were observed, 5/50 had 2 doses, and 32/50 had 3 doses. The time since the last PCV varied from 7 to 102 months. No significant differences in pre- and post-PPV23 antibodies were observed according to PCV dose (Figure 2, C) and time since the last PCV (Figure 2, D).

Screening for SAD and other antibody deficiencies

3 cases of poor post-PPV23 anti-pneumococcal response were observed, already described in the previous section: patients N°4 and 5 with post-PPV23 levels < 110 mg/L, and patient N°17 with a post/pre-PPV23 increase of 1.5. However, only two of these patients were classified as SAD cases, while the third case was defined as a CVID. In summary, according to the definitions used in this study for antibody deficiencies, the clinical-immunological phenotype for patient N°5 was compatible with CVID (decreased serum IgA and IgG, with deficient anti-pneumococcal response) and, in patients N°4 and 17, the presence of SAD was established (deficient anti-pneumococcal response with normal IgA, IgG, IgM, and IgG subclasses). Thus, the frequency of SAD in this study was 4% (2/50).

Other antibody deficiencies were detected: 2 cases of IgAD in patients N° 2 and 21; 2 cases of IgGSD associated with IgAD in patients N° 8 and 39; 5 cases of isolated IgGD in patients N° 15, 27, 32, 42, and 46 (patients N° 27 and 42 with decreased IgG subclasses). IgGDs can be classified as unspecified hypogammaglobulinemia and, in children aged under 5 years (N° 15 and 42), it could be a transient hypogammaglobu-

Table 1. Clinical-demographic characterization of the study population (n = 50)

Characteristics	Frecuency (n)	Percentage (%)
Male/Female	26/24	52.0/48.0
Origin		
Central Department	26	52.0
Cities in the interior of country	16	32.0
Asunción (Capital city)	8	16.0
Educational status (n = 32)*		
No frequent absences from school	18	56.3
Frequent absences due to RI	13	40.6
Left school due to RI	1	3.1
Clinical manifestation (2 episodes/year)		
URTI (tonsillitis, pharyngitis and/or laryngitis)	35	70.0
LRTI (bronchitis and/or pneumonia)	31	62.0
Otitis and/or sinusitis	17	34.0
Lymphadenopathy (inflammation and/or infection of lymph nodes)	16	32.0
Fever without determined etiology	15	30.0
Skin infections	11	22.0
Gastrointestinal and/or urinary infection	9	18.0
Severe infection and/or severity factor (at least one episode)		
Sepsis	9	18.0
Severe pneumonia (pleural effusion, abscess and/or necrosis)	6	12.0
Abscesses (skin and/or organs)	3	6.0
Intravenous antibiotics (at least once in the last year)	43	86.0
Hospitalization (at least once in the last year)	44	88.0
Admission to intensive care unit (ICU)	12	24.0
Allergic disease		
Asthma	13	26.0
Allergic rhinitis	15	30.0
Asthma and allergic rhinitis	5	10.0
AD with/without CMPA	5	10.0
Family history related to IEI		
Family member (father, mother and/or brother) with allergies	19	38.0
Brother/sister with RI	12	24.0
Unexplained early infant death	4	8.0
Case of IEI in the family	2	4.0
Diagnosis and/or treatment (at the time of the study)		
No diagnosis	21	42.0
Allergy diagnosis	25	50.0
Autoimmune pathology (Celiac disease and ITP)	2	4.0
Treatment with anti-allergy	26	52.0
Antibiotic treatment	5	10.0

URTI: upper respiratory tract infections; LRTI: lower respiratory tract infections; AR: allergic rhinitis; AD: atopic dermatitis; CMPA: cow's milk protein allergy; ITP: immune thrombocytopenic purpura; IR: recurrent infections; IEI: inborn errors of immunity; *: patients of starting school age.

Table 2. Anti-pneumococcal antibodies and serum immunoglobulins in the pediatric population with recurrent infections (n = 50)

Determination	Median	IQR	Total range
Anti-pneumococcal pre-PPV23, mg/L	46.8	23.6-73.5	2.3-168.7
Anti-pneumococcal post-PPV23, mg/L	298.1	247.1-381.6	37.7-495.3
Increased anti-pneumococcal post/pre-PPV23	6.1	4.6-12.2	1.5-77.1
Weeks (days) post-PPV23	4 (28)	4-5 (28-30)	4-6 (25-39)
Immunoglobulin A (IgA), mg/dL	94.2	40.9-128.5	8.6-331.0
Immunoglobulin G (IgG), mg/dL	836.2	686.6-948.1	192.3-1553.1
Immunoglobulin M (IgM), mg/dL	132.7	104.0-168.0	47.4-331.5
Immunoglobulin E (IgE), IU/mL	91.5	25.2-307.8	1.1-928.3
IgG subclass 1 (IgG1), g/L	5.63	5.09-6.87	1.50-13.12
IgG subclass 2 (IgG2), g/L	2.08	1.54-2.65	0.38-5.58
IgG subclass 3 (IgG3), g/L	0.49	0.38-0.65	0.08-1.43
IgG subclass 4 (IgG4), g/L	0.29	0.14-0.49	0.01-1.65

IQR: interquartile range.

linemia of infancy (THI). The total frequency of antibody deficiencies in our cohort was 24.0% (12/50). Table 3 summarizes the clinical-immunologic phenotype of patients with SAD and other antibody deficiencies detected in this study.

Discussion

Antibody deficiencies constitute the most frequent IEI in the pediatric population. This group includes specific antibody deficiency (SAD), characterized by a deficient anti-pneumococcal response[14]. In this work, a pediatric population with RI was evaluated for SAD and other antibody deficiencies by studying the post-PPV23 anti-pneumococcal response and serum immunoglobulins. We observed a median age of 5 years and a slight predominance of males. Previous studies[15-17] reported similar data. Most of our patients were from the Central Department and more distant cities (country's interior); in fact, the hospitals where they were recruited concentrate patients from all over the country (public referral centers). Recurrent respiratory infections predominated in our cohort, which is consistent with previously reported data[16]. Another frequent clinical characteristic was allergy, considered a predisposing factor for recurrent respiratory tract infections[18].

For pre-PPV23 anti-pneumococcal antibodies, the age distribution showed medians ranging from 29.8 to 66.0 mg/L. Parker et al[19] obtained similar results in adults. Higher averages of up to 116.6 mg/L were reported in healthy children[13]. It is known that the response to polysaccharides antigens is very heterogeneous, varying with age, immunity, and also between individuals of the same age group[4]. On the other hand, we observed 17 children with pre-PPV23 levels ≤ 27.5 mg/L, a value reported as protective[13]; 12 of them had complete PCV schedule, therefore, in our population, the protective value would be different from that reported. However, 4 of these children presented values ≤ 10.0 mg/L, considering that they had PCV, these cases would correspond to PCV-non-responders[7].

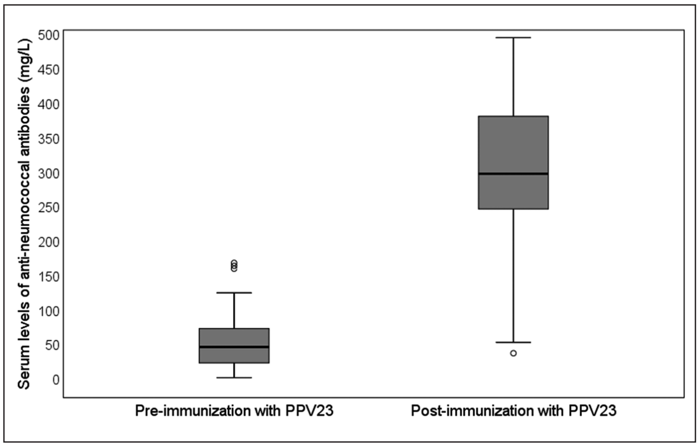

Figure 1. Anti-pneumococcal antibodies pre- and post-PPV23 (n = 50). A significant increase ($p < 0.001$; Wilcoxon test) in post-PPV23 levels was observed, except for two patients with post-PPV23 values < 110 mg/L (point under the "box"). Three patients were also observed with pre-PPV23 levels > 110 mg/L (points above the "box").

For the post-PPV23 anti-pneumococcal response, we observed a median of 298.1 mg/L and an increase of 6.1. Parker et al[12], reported an increase of 9 and a median of 375 mg/L in healthy adults. In adults with RI, medians between 100 and 300 mg/L were reported[11,20]. The anti-pneumococcal response depends on vaccination history, previous exposure to pneumococcus, immune system status of each individual, pneumococcal serotypes, and age[21], therefore, discrepancies between different studies are expected. We found no reports describing post-PPV23 antibodies in children with RI, evaluated by global ELISA; previous studies from other countries, evaluated anti-serotype antibodies by WHO-ELISA and/or multiplex assays[7].

In relation to the 17 patients with pre-PPV23 antibodies ≤ 27.5 mg/L, 16 of them responded adequately to PPV23. Many children who fail to respond to 3 or 4 PCV doses, respond to one dose of PPV23, leading to their clinical improvement[22]. Besides, age is a factor that influences the response to pneumococcus. Previous studies in children reported that pre-PPV23 antibody levels increased with age[13] In our series, we did not observe significant differences with age, which could be due to the small sample size and the study of a global and not serotype-specific anti-pneumococcal response.

In this study, we were able to detect two cases of SAD. In one of them, the patient presented post-PPV23 antibodies < 110 mg/L; this cut-off point was established in adults[11]. Janssen et al. reported a post-PPV23 value of 96.1 mg/L for "good responders" in a population of adults and children with no history of PCV[23]. Patients with post-PPV23 levels > 110 mg/L and with

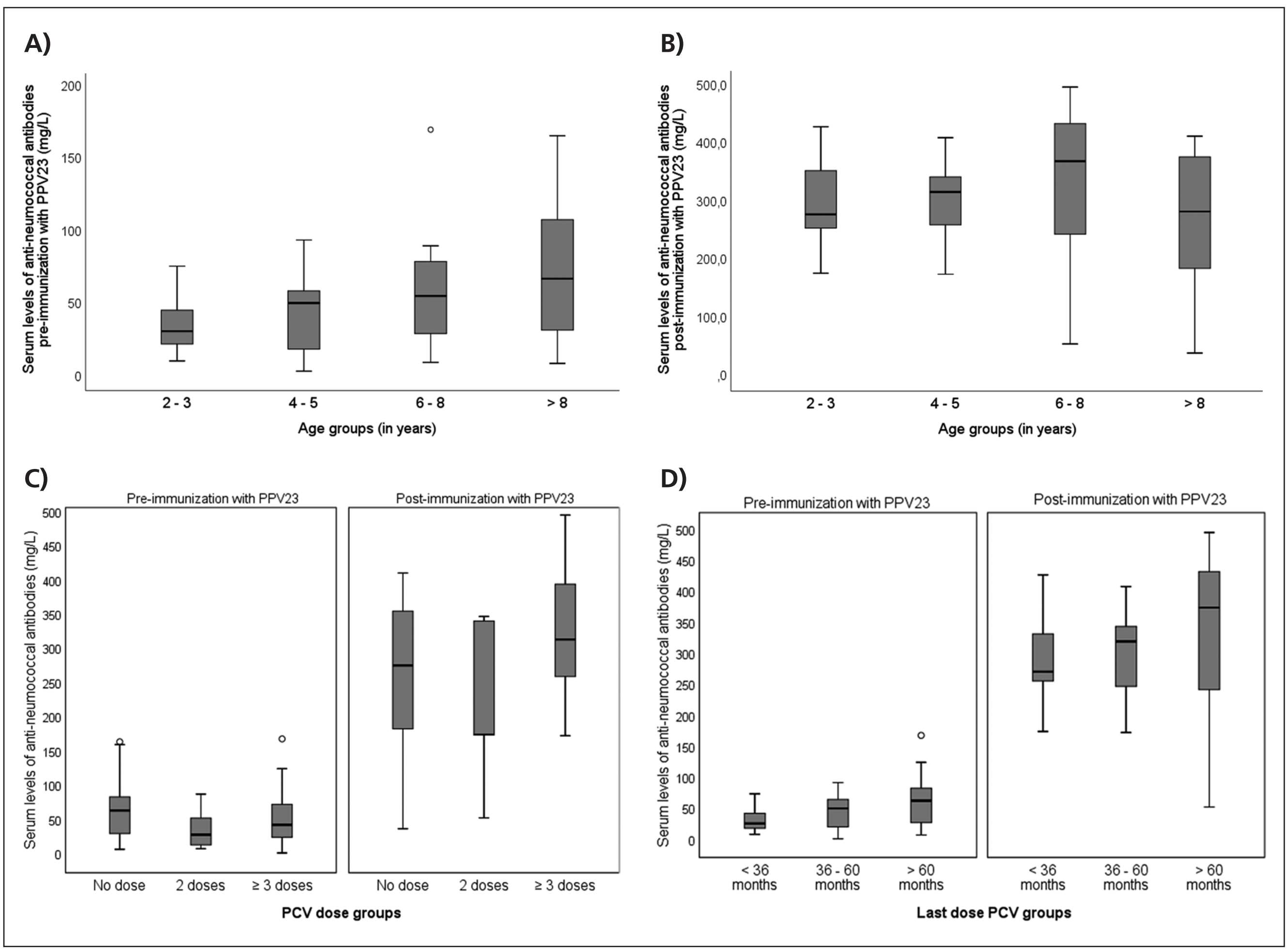

Figure 2. Anti-pneumococcal response according to age and PCV. A) Pre-PPV23 antibodies according to age groups: slight increasing trend with increasing age, but without significant difference (p = 0.138; Kruskal-Wallis Test). B) Post-PPV23 antibodies according to age groups: slight tendency of increase until the 6–8-year-old group and then a decrease, however, the difference was not significant (p = 0.585; Kruskal-Wallis Test). C) Pre- and post-PPV23 antibodies according to previous doses of PCV: no significant differences were observed between pre-PPV23 levels (p = 0.391; Kruskal-Wallis Test), nor were there differences between post-PPV23 levels (p = 0.135; Kruskal-Wallis Test). D) Antibodies pre- and post-PPV23 according to time of the last PCV: no significant differences were observed between levels pre-PPV23 (p = 0.102; Kruskal-Wallis Test), nor post-PPV23 (p = 0.356; Kruskal-Wallis Test).

Table 3. Clinical-immunological phenotype of patients with SAD and other antibody deficiencies detected in this study (n = 12)

N°	Age*/ Sex	RI (age of onset*)	Infect./ year	Hospital/ year (days)	Severe infection/ ICU	Allergy/ Family history	IgA mg/dL	IgG mg/dL	IgM mg/dL	IgE UI/mL	IgG1 g/L	IgG2 g/L	IgG3 g/L	IgG4 g/L	Pre-PPV23 mg/L	Post-PPV23 mg/L	PAD
2	4/M	URT (4)	2	1 (43)	Sepsis/Yes	AR/Family with allergy	**16.9**	841.8	159.7	27.3	6.59	1.58	0.25	0.13	88.1	340.9	IgAD
4	17/F	Abscesses (7)	10	4 (20)	Sepsis/Yes	AR/Siblings with RI	203.4	881.5	213.5	64.7	4.80	3.48	0.83	0.07	7.61	**37.7**	SAD
5	7/F	Pneumonia (2)	5	5 (10)	Sepsis/Yes	Asthma/Early infant death	**8.6**	**316.2**	47.4	2.0	4.35	1.75	0.16	0.02	28.9	**53.5**	CVID**
8	11/F	URT (9)	3	1 (7)	Candidiasis/ No	FA/Family with allergy	**58.4**	789.1	90.4	121.4	**4.12**	2.14	0.43	0.37	88.3	276.2	IgGSD+ IgAD
15	4/M	LRT (0,5)	2	1 (4)	No/No	Asthma+AR/No	107.2	**540.3**	96.2	602.9	5.38	0.78	0.27	0.19	17.5	213.3	IgGD
17	13/M	Fever wf. (10)	4	1 (8)	Sepsis/No	AR/Siblings with RI	111.0	1.238.3	141.0	806.6	13.12	2.41	0.46	1.22	**160.4**	**247.1**#	SAD
21	2/F	URT (0,5)	4	1 (5)	No/No	AD+CMPA/ Family with allergy	**16.3**	524.5	103.0	3.9	4.23	0.79	0.49	0.05	44.3	261.6	IgAD
27	8/F	Pneumonia (2)	3	3 (7)	Severe peumonia/No	Asthma/Siblings with RI	94.2	**430.6**	228.5	880.4	**2.43**	1.76	0.56	0.08	168.7	348.2	IgGD##
32	5/M	Otitis (1)	3	2 (7)	No/No	AR/Siblings with RI	86.0	**524.5**	109.1	439.0	3.95	2.04	0.45	0.04	55.4	394.7	IgGD
39	17/M	Abscesses (13)	6	2 (10)	Sepsis/No	No/Family case of IEI	**82.1**	1234.2	121.5	25.2	7.79	4.29	**0.16**	0.14	37.6	411.2	IgGSD+ IgAD
42	2/F	Pneumonia (2)	2	2 (7)	Severe peumonía/ Yes	AD+CMPA/ Family with allergy	27.3	**192.3**	59.3	928.3	**1.50**	0.38	**0.08**	**0.01**	20.9	427.3	IgGD##
46	11/F	Skin (7)	4	1 (3)	Abscesses/No	AR/Siblings with RI	101.0	**508.0**	168.0	45.9	5.49	1.12	0.223	0.20	23.6	120.1	IgGD

*en años; M: masculino; F: femenino; IR: infecciones recurrentes; sf.: sin foco; Infecc.: infecciones; Hospit.: hospitalizaciones; UCI: Unidad de cuidados intensivos; Antecc.: antecedente; Fliar.: amiliar; Herno.: hermano/a; RA: rinitis alérgica; AA: alergia a alimentos; DA: dermatitis atópica; APLV: alergia a proteínas de leche de vaca; DPA: deficiencia predominante de anticuerpos; DIgA: deficiencia de IgA; CVID**: inmunodeficiencia común variable con respuesta anti-neumococo deficiente; SAD: deficiencia de anticuerpos específicos; DIgG: deficiencia aislada de IgG: #incremento post/pre=1,5; ##con subclases de IgG disminuidas. En negrita y subrayado, los valores de anticuerpos por debajo de lo normal o respuesta anti-neumococo deficiente.

clinical characteristics highly suggestive of SAD should be evaluated for anti-serotype antibodies, considering the limited sensitivity of the global ELISA[7,11]. This determination (WHO-ELISA or multiplex assays) is not available in Paraguay, due to its high cost and difficulty of implementation; currently, it is available only in highly qualified laboratories in other countries[7]. The other SAD case in our series presented a post-PPV23 increase of < 2. Regarding global ELISA, we did not find recommendations on cut-off points in children with elevated pre-PPV23 antibodies; however, Parker et al[12], reported increases of ≥ 2 in healthy adults.

SAD is generally observed in 11.0% to 23.1% of patients with recurrent respiratory infections[16]. In this study, its low frequency (4.0%) could be due to the small sample size and the use of the global ELISA (probability of false negatives)[7]. Despite this, it is a widespread assay in routine clinical laboratories and when compared to the WHO-ELISA, Lopez et al. concluded that it is diagnostically useful, to then study anti-serotype antibodies on a case-by-case basis[11]. Despite the limitation of the global ELISA, the cases detected and the frequency established in this study constitute the first SAD data in Paraguay, which provides knowledge to local pediatricians, highlighting the importance of evaluating the anti-pneumococcal response in children with RI.

We also detected other antibody deficiencies such as 1 case of CVID, 2 cases of IgAD, 2 cases of IgGSD associated with IgAD, and 5 cases of IgGD. A previous retrospective study performed in children[17], showed IgAD and CVID as the most frequent and IgGD was not observed. The IgAD in this study would be partial (IgA > 7 mg/L but below normal) and one case would be transient (age < 4 years)[24]. It is important to follow-up patients with IgAD, as it may progress to CVID and/or present autoimmunity[25]. IgGD was the most frequent; the AAAAI classifies this deficiency as unspecified hypogammaglobulinemia, and in children aged under 5 years it could correspond to transient hypogammaglobulinemia[1]. We detected IgGSD associated with IgAD; previous studies we performed did not include the evaluation of subclasses[17]. In our country, the evaluation of IgG subclasses is only available in private laboratories and at high costs, which makes its study difficult.

Finally, we characterized the 12 patients with antibody deficiencies. Respiratory infections and allergies predominated, we also observed sepsis and severe pneumonia, which was previously reported[9]. The median age at the onset of infections was 2 years and, considering the age at the time of the study as the age of diagnosis (Median: 6 years); the 4-year difference would correspond to a delay in diagnosis; similar data were observed in a study from Argentina[26]. Regarding our SAD cases, abscesses and adenopathies were frequent, we also documented upper respiratory infections, sinusitis, allergy, and severe infection, which is consistent with previous reports[5,27]. Regarding treatment for SAD and other deficiencies such as CVID and IgGD, experts recommend antibiotic prophylaxis, management of other conditions such as asthma, allergic rhinitis, and chronic rhinosinusitis, increased monitoring, appropriate antibiotic therapy for infections, immunization with PCV, and human intravenous immunoglobulin replacement therapy[7,14].

This study had limitations. We evaluated a reduced sample size since the COVID-19 pandemic (2020-2021) affected patient recruitment. In addition, the anti-serotype antibody study is not available in Paraguay, and it was not possible to implement the WHO-ELISA due to its high cost. The low frequency of SAD could be due to the determination of a global response. The post-PPV23 antibody criterion ≤ 110 mg/L was reported for adults, however, we did not find a cut-off point for the global ELISA in children with PCV history, which could have affected the detection of SAD.

Conclusion

We detected two cases of SAD and other deficiencies such as CVID, IgAD, IgGD, and IgGSD associated with IgAD. Thus, we implemented the diagnostic technique for specific antibody deficiency and provided the first data in Paraguay. Additionally, we provide information on pre-PPV23 antibodies generated in response to PCV, and the post-PPV23 increase, either for diagnostic or protective purposes. We also observed a delay of approximately 4 years in the detection of antibody deficiency, so we need to continue strengthening our knowledge about these pathologies to improve suspicion, diagnosis, and timely treatment.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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