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CASE SERIES

Specific antibody deficiency: Primary immunodeficiency associated to respiratory allergy

Deficiencia de anticuerpos específicos: inmunodeficiencia primaria asociada a alergia respiratoria

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Abstract

Introduction: Specific antibody deficiency (SAD) with normal immunoglobulin and normal B cells is a primary immunodeficiency characterized by reduced ability to produce antibodies to specific antigens especially polysaccharides. **Objective:** To describe the characteristics of patients diagnosed with SAD emphasizing the association between primary immunodeficiency and allergic diseases. **Patients and Method:** Descriptive study showing patients with SAD treated at a public hospital between August 2007 and July 2015. Other secondary or primary immunodeficiency was discarded. The diagnosis of SAD was based on recurrent infections and abnormal response to pneumococcal polysaccharide vaccine assessed by specific IgG to 10 pneumococcal serotypes. **Results:** Twelve patients were included, 4 males, mean age 6 years. Recurrent pneumonia was the most common disease (91.7%) as well as other respiratory and invasive infections. All patients had associated asthma, 11 had allergic rhinitis, and other allergies. Three patients did not respond to any of the 10 serotypes contained in pneumococcal polysaccharide vaccine, and responders patients showed response to low titers. Treatment with conjugate pneumococcal vaccine was favorable in 11/12 patients. **Conclusion:** In children older than 2 years with recurrent respiratory infections or invasive *S. pneumoniae* infections with normal immunoglobulin we recommend to investigate SAD, especially if they have a concurrent allergic disease.

Keywords:
Allergy;
Asthma;
Pneumococcal vaccine;
Primary immunodeficiency;
Specific antibody deficiency

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Introduction

Specific antibody deficiency (SAD) is a type of primary immunodeficiency (PID)[1] characterized by inadequate production of antibodies against polysaccharide antigens in individuals who have a normal response to protein antigens, normal levels of Immunoglobulins (Ig) and subclasses of IgG and a normal number of B lymphocytes[2]. It is known that the response to polysaccharide antigens matures with age, so it could correspond to a delay in the maturation of the immune system. However, when the patient has a recurrent infection clinic or the need for frequent antibiotic use, there is most likely to be a defect in the immune response that has not yet been recognized.

It corresponds to one of the most frequent immunologic defects in patients with recurrent infections and/or sinopulmonary infections, with reports ranging from 11 to 23.1% of these cases in children [2,3] and even in a cohort study of 24 children with chronic wet cough have reported a prevalence as high as 58%[4]. The diagnosis is made in children older than 2 years, with an inadequate response to non-conjugated pneumococcal vaccine defined as levels of post-immunization antibodies lower than 1.3 µg/mL as measured by a suitable and reliable technique, in more than 50% of the serotypes tested in children between 2-5 years and over 70% for those older than 5 years[5]. A percentage of patients with SAD may have an associated allergic disease, so failure to respond to appropriate treatment should lead to suspicion of this clinical entity, especially if they have recurrent infections[6].

The objective of this study is to describe the demographic and clinical characteristics of a group of patients diagnosed with SAD in control at a reference center for immunodeficiencies and to highlight the association between a PID and allergic diseases.

Patients and Method

Descriptive study of patients with confirmed diagnosis of SAD in control in the immunology polyclinic of the Dr. Exequiel González Cortés Hospital between August 2007 and July 2015. We analyzed the clinical data recorded in each patient's clinical record, such as: epidemiological background, comorbidities, clinical manifestations, laboratory tests, evaluation of the response to polysaccharide antigens, and management.

Inclusion criteria

1) age between 2 and 18 years; 2) normal levels of Ig and subclasses of IgG; 3) not having previously received the pneumococcal vaccine, and 4) formal evaluation of the antibody response to the unconjugated pneumococcal vaccine between 45 and 60 days after immunization.

A complete blood count with neutrophil and lymphocyte absolute counts, serum G, M, A and E immunoglobulin, C3 complement, and IgG subclasses were performed in all patients. All values were classified as normal if they were within 2 standard deviations from the mean for the age. Anti-polysaccharide-specific IgG antibodies from 10 pneumococcal serotypes (S1, S3, S4, S5, S6, S9, S14, S18C, S19F and S23F) were measured by third generation ELISA calibrated and preabsorbed according to the standardized CDC technique[7]. The post-immunization response was considered normal if values were greater than 1.3ug/mL for more than 50% of serotypes in children aged 2 to 5 years and more than 70% of serotypes in children older than 5 years. The diagnosis of SAD was based on the history of recurrent infections with normal IgG, IgM, IgA and IgG subclasses and with abnormal IgG antibody responses against the pneumococcal polysaccharide vaccine.

Results

Data were analyzed for 12 patients, of whom 8 (66.7%) were women; The average age at diagnosis was 6 years (range 3 to 11), with 66.7% (n = 8) older than 5 years. None of the patients had a history of consanguinity in the parents, family history of PID, or dead children under the age of one year.

The most frequent presentation was recurrent infections, mainly pneumonia in 91.7% (n = 11) of the patients, 3 of which also had a history of recurrent otitis (more than 4 a year) and one, septic arthritis of knee antecedent, without isolated germ. Only one patient had a history of invasive infection with encapsulated agents with pneumococcal meningitis.

Among comorbidities, 91.7% (n = 11) were carriers of allergic rhinitis and 100% of the patients were controlled for recurrent wheezing and asthma; One patient also had atopic dermatitis and another patient had multiple food allergies as concomitant diseases (table 1). Table 2 shows the results of other immunological evaluation tests.

Twenty five per cent 25% (n = 3) of the patients had no response to any of the 10 serotypes measured after the administration of the pneumococcal polysaccharide vaccine. Another 25% (n = 3) had a response between one and two serotypes, and the remaining 50% (n = 6), all older than 5 years, responded between 4 and 6 pneumococcal serotypes (table 3). Of the serotypes with response (n = 24), the majority (66.7%, n = 16) had low response titers (between 1.3-2 µg/mL) and 33.3% (n = 8) had a slightly greater response to

Table 1. Main clinical characteristic of patients

Patient	Age (years)/sex	Infections	Admissions	Vaccine responses: serotypes (n)	Comorbidity
1	3/M	Pneumonia (2)	0	0	Asthma
2	3/F	Pneumonia (2), eptic arthritis (1)	1	1	Asthma, AR
3	4/F	Pneumonia (5), AO (4)	4	0	Asthma, AR
4	4/M	Pneumonia (4)		2	Asthma, AR
5	5/M	Pneumonia (2)	1	4	Asthma, AR
6	6/F	Pneumonia (2)	1	6	Asthma, AR
7	6/M	Pneumonia (2), AO (4)	> 12	2	Asthma, AR
8	9/F	Pneumococci Meningitis (1)	1	0	Asthma, AR
9	11/F	Pneumonia (> 2 year)	0	5	Asthma, AR, AD
10	6/F	Pneumonia (3), AO	2	3	Asthma, AR, FA
11	9/F	Pneumonia (4)	2	2	Asthma, AR
12	9/F	Pneumonia (3)	1	4	Asthma, AR

AD: atopic dermatitis; AO: acute otitis; AR: allergic rhinitis; F: female; M: male; n: number.

Table 2. Mean values of main immunologic analysis

Leucocyte count/mm^3	9.780
Neutrophil count/mm^3	4.966
Lymphocyte count/mm^3	3.838
Serum Immunoglobulin G, mg/dL	772
Serum Immunoglobulin M, mg/dL	127
Serum Immunoglobulin A, mg/dL	107
Serum Immunoglobulin E, mg/dL	11
C3Complement, mg/dL	126.5
C4 Complement, mg/dL	21.5
T Lymphocytes CD3+, %	70.3
T Lymphocytes CD4+, %	44
T Lymphocytes CD8+, %	28
NK cells CD56+, %	9
B Lymphocytes CD19+, %	15

Table 3. Number of positive responses (> 1.3 µg/mL specific IgG) to pneumococcal antigens

Number of responses	Patients under 5 years age (n = 4)	Patients over 5 years age (n = 8)
0	2	1
1	1	0
2	1	1
3	0	0
4	0	3
5	0	2
6	0	1
7	0	0

Table 4. Number and percentages of positive responses (> 1.3 µg/mL specific IgG) to each polysaccharide pneumococcal antigens

Serotype	Positive responses, n (%)
1	0 (0)
3	4 (33.3)
4	3 (25)
5	5 (41.7)
6B (26)	6 (50)
9V (68)	1 (8.3)
14	3 (25)
18C (56)	2 (16.7)
19F	4 (33.3)
23F	2 (16.7)

2 µg/mL (between 2.1-2.6 µg/mL). Regarding the specific serotype response, 100% (n = 12) of the patients did not respond to serotype 1 (table 4).

Subsequent to the diagnostic confirmation of SAD, all patients were given a 10-valent pneumococcal conjugate vaccine (PCV10, Synflorix®, GSK) or 13 valent (PCV13, Prevenar®, Abbott) as part of the treatment, in addition to their allergic disease corresponding management (avoidance of allergens, elimination diet, bronchodilators, inhaled corticosteroids, antihistamines, skin care). None of the patients required Ig administration at replacement doses. A patient (patient 8)

persisted with recurrent infections, so a new dose of non-conjugated pneumococcal vaccine (Pneumo23®, Pasteur Mérieux) was administered with a post-vaccine antibody titer that revealed a response to 9/10 serotypes and an excellent clinical response.

Discussion

The first descriptions of antibody deficiency syndrome with normal Ig count, as it was initially known, were performed by Saxon et al.[8] in 1980 through the report of 2 cases of patients with recurrent infections and an inadequate response to protein antigens. Thereafter, there have been multiple reports in the literature describing groups of patients with a poor response to polysaccharide antigens associated or not with another PID[9,10].

In other primary immunodeficiencies, this inability to respond adequately to polysaccharide antigens has been described in patients with Wiskott-Aldrich syndrome, partial DiGeorge syndrome, asplenic, hyper-IgE syndrome, and those with selective IgA deficiency without subclass deficits. In addition, SAD can be found in patients with dysmorphic syndromes or chromosomal abnormalities associated with recurrent infections and conditions that cause immunosuppression, such as immunosuppressive therapy, chronic lung disease, caloric-protein malnutrition and HIV, among others. The case of a patient with a mutation of Bruton's tyrosine kinase with normal Ig count but with an inadequate response to polysaccharide antigens has been described[11]. In the patients presented here, other PIDs were reasonably ruled out.

The inheritance pattern and pathogenesis of this condition have not been fully elucidated, and due to the great variability of clinical manifestations it is believed that different defects may result in this condition. A defect or the absence of a subpopulation of B lymphocytes or suppressive T lymphocytes has been raised against specific antigens[12].

A recent publication by Leiva et al.[13] determined the different subtypes of memory B lymphocytes in healthy children and in children with recurrent infections with or without SAD. At the same time, patients with SAD were classified according to the non-response to polysaccharide antigens in PPV-SAD and those with alteration in the response to PCV-SAD conjugated antigens. It was found that patients with PPV-SAD had a decrease in isotype-shifted memory B lymphocytes and IgM + memory B lymphocytes versus control groups, children with recurrent infections but without SAD and PCV-SAD. This is related to differences in antigen presentation mechanisms dependent on the nature of the antigen. The authors suggest that patients with PPV-SAD may have a defect in the developmental pathway of IgM memory B lymphocytes

This study focused on those patients with an inadequate response to polysaccharide antigens with no other associated immunodeficiency. The main form of clinical manifestation that led to the diagnosis of SAD in this series were recurrent infections of the respiratory tract. This is similar to that reported by other authors[2,10,14], where, like other immunodeficiencies in which the humoral response is affected, recurrent respiratory infections are the predominant clinical manifestation. In this study, most patients presented as recurrent pneumonia, unlike other publications in which upper respiratory tract infections, such as media acute otitis[2,6] or sinusitis[15], were the most frequent form of presentation. However, it is important to note that this entity should also be considered in patients with severe infections, as was the case of the patient who manifested pneumococcal meningitis.

Similar to other studies[6,14], all children in this series had at least one form of associated allergic disease, mainly asthma and allergic rhinitis. In an earlier series reported by our group with 8 patients not included in this study, we found this same association[14]. It could be argued that SAD may represent a form of immune dysregulation that leads to an inadequate response to both pathogens and innocuous environmental antigens for the majority of the population.

For the diagnosis the measurement of ideally 14 serotype titers is recommended after administration of the pneumococcal polysaccharide vaccine and including at least 7 serotypes present only in the polysaccharide 23-valent vaccine, being considered protective values of infection and colonization levels greater than 1.3 μg/mL[16,17]. In Chile, the measurement of 10 serotypes (1, 3, 4, 5, 6B, 9V, 14C, 19F, 23F) are available, of which only serotype 3 is not present in the 10-valent vaccine (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F), currently included in the National Immunization Program since January 2011. This aspect is important to consider for the proper diagnosis of children with recurrent infections born after November 1, 2010, being described in the literature a group of patients with a specific antibody deficit that only affects the pneumococcal polysaccharide conjugate antigens (PCV-SAD)[13].

According to one publication of the American Academy of Allergy, Asthma and Immunology working group regarding the interpretation of diagnostic vaccination in PID, it ranks according to the degree of non-response to the vaccine in 4 phenotypes, from a memory phenotype to mild, moderate and severe forms[5]. It should be noted that 83.3% of our patients had a severe phenotype, reaching protective levels in no more than 2 serotypes and with low levels (< 1.3-2 μg/mL).

In this group we found more severe or serious forms of presentation.

Regarding the response to specific serotypes, some publications have tried to establish whether the non-response to a serotype can predict the diagnosis of SAD. The Boyle et al.[6] group showed that there is a greater risk of SAD when there is no response to serotypes 4, 9V, 15 or 23F, being this particularly true for serotype 23 since none of its patients was able to demonstrate a response against this serotype. In our patients, 100% did not reach protective levels against serotype 1 and only between 1 or 2 patients did so for serotypes 4, 9V and 23F, which is similar to that published by Boyle et al. They also establish that the response to 2 or more of these serotypes has a negative predictive value of 98% and they evidence that a protective response to less than 2 of the 4 indicated serotypes is sufficient to confirm the diagnosis of SAD in children with recurrent infections. This could eventually be useful in reducing the cost of testing by testing fewer serotypes, but it should be validated through further studies involving a greater number of patients.

Management consists in the administration of pneumococcal conjugate vaccine based on studies that demonstrated that the vaccine is capable of inducing an IgG response in 80 to 90% of children with recurrent infections who do not respond to the polysaccharide vaccine[17], presenting a clinical improvement. It should be kept in mind that the vaccine only confers protection against the 10 or 13 most common serotypes included in it, being also the treatment of the basic allergic disease a fundamental mainstay.

In severe cases of SAD, the use of intravenous immunoglobulin (IGEV) in replacement doses may be considered. However, there is concern that eventually the use of IGEV could interfere in the development of the immune system response. Contrary to this, there is a publication that suggests that the use of IGEV may have an immunomodulatory effect *in vitro* on the production of IgG and cytokine antibodies associated with a Th1/Th2 balance-regulating mechanism, supported also by the observations made by that same group that in children treated with IGEV for a period of up to 2 years, upon cessation of therapy, the antibody response improved either spontaneously or after the administration of the 23-valent vaccine[18].

In summary, SAD is a frequent PID that manifests itself as recurrent respiratory infections and, in some cases, as severe infections and, in most patients, it is associated with an allergic disease, so in allergic patients with recurrent infections it is recommended to consider and investigate this diagnosis. For the study, a quantification of Ig and a measurement of specific anti-pneumococcal antibodies is performed after the administration of the 23-valent vaccine. The majority of patients respond to the administration of the conjugate vaccine, being this a highly cost-effective therapeutic alternative.

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.

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Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

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