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SPECIFIC ANTIBODY DEFICIENCY IN PEDIATRIC PATIENTS WITH RECURRENT RESPIRATORY INFECTIONS

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ABSTRACT

One of the most frequent consultations in pediatric immunology corresponds to patients with recurrent respiratory infections. The most frequent clinical conditions consultations are recurrent viral infections, recurrent acute otitis media, recurrent sinusitis and recurrent pneumonia. Approximately 10% of patients who consult for these conditions may have a specific antibody deficiency. Specific antibody deficiency is a type of primary immunodeficiency, which is classified within the humoral deficit group, where there is a failure in the immune response for polysaccharide antigens with normal immunoglobulin levels. The diagnosis must be made after turning 2, when the immune system acquires the ability to present a humoral immune response to polysaccharide antigens. In an undetermined percentage of patients, the specific antibody deficit can be resolved with the maturity of the immune system and there are patients who require prolonged treatment with antibiotic prophylaxis and gamma globulin.

Key words: antibodies deficiency, pneumonia, respiratory tract infection.

INTRODUCTION

Specific antibody deficiency (SAD) is defined as the inability to have antibody-mediated immune response to the administration of the pneumococcal polysaccharide vaccine, with normal immunoglobulin levels (1). It has been described that between 7-19% of patients with recurrent infections have SAD. Depending on the different series (2-3), patients with SAD present with more frequency infections such as sinusitis, acute otitis media and pneumonia (4).

Because the immune response to polysaccharide antigens is generated after 2 years of age, the unconjugated pneumococcal vaccine should be administered after turning 2, and only after administration of the vaccine or after a pneumococcal invasive infection can we measure response and make the diagnosis of SAD. It is also important to remember that what is being measured is an independent T lymphocyte response, this means that the antigen is presented directly to the B lymphocyte and the presence of the T lymphocyte is not required to generate antibodies. Currently in our country there is vaccination program at 2, 4 and 12 months with pneumococcal conjugate vaccine against 13 serotypes, implemented programmatically since 2017 for all of Chile, which induces a T-dependent response.

We will continue detailing the steps to follow to make an adequate diagnosis of SAD and we will also review the management of this disease with the available evidence.

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IMMUNOLOGICAL EVALUATION IN PATIENTS WITH RECURRENT INFECTIONS

Recurrent infections are a frequent cause of consultation in immunology, the majority correspond to patients with high respiratory conditions in patients younger than 4. It should be noted that a healthy patient without any immune deficiency can present on average 8 (up to 12) viral respiratory episodes in the year, which is within normal range. A very detailed medical history of the infectious conditions that the patient has presented and the severity they have had must be detailed to guide the exams in the best possible way and not request very expensive laboratory studies that will not play a significant role in our patient.

In addition, some background in the patient's history such as asthma, allergic rhinitis and another manifestation of atopy such as atopic dermatitis should be considered and we must request their immunization summary to see the number of doses of pneumococcal conjugate vaccine.

In order to carry out the evaluation of a patient with suspected SAD, it is necessary to consult, in a directed way by history and number of episodes, the following: acute otitis media (AOM), sinusitis, bacterial pneumonia and complicated pneumonia. If the described episodes correspond to more than 3 AOM in a year, 2 sinusitis in a year, 2 bacterial pneumonia and 1 complicated pneumonia, the patient requires immunological evaluation. It should be considered that any of these constitutes an alert for immunological studies. In these patients, immunoglobulin counts (IgG, IgA, IgM, total IgE), hemolytic complement activation (CH50), lymphocyte subpopulations and pneumococcal antibodies are usually requested (5).

PNEUMOCOCCAL ANTIBODY MEASUREMENT TECHNIQUES

There are currently two techniques to carry out the study of pneumococcal antibodies: ELISA and Luminex. The most used method corresponds to the World Health Organization ELISA test (WHO ELISA), initially available to perform 7 pneumococcal serotypes, currently available for the 23 serotypes covered by the polysaccharide vaccine. In Chile, it is available for the measurement of the 13 serotypes comprising the pneumococcal conjugate vaccine Prevenar13® (Table 1).

Table 1. 23 serotypes of Streptococcus pneumoniae covered by pneumococcal polysaccharide conjugate vaccine (Prevenar13®)

Serotype	PPSV 23	PCV 13
1	X	X
2	X	
3	X	X
4	X	X
5	X	X
6A		X
6B	X	X
7F	X	X
8	X	
9N	X	
9V	X	X
10A	X	
11A	X	
12F	X	
14	X	X
15B	X	
17F	X	
18C	X	X
19A	X	X
19F	X	X
20	X	
22F	X	
23F	x	X
33F	X	

Antibodies measured by ELISA are expressed in µg / ml and detect up to levels of 0.35 µg / ml. Currently, above 1.3 µg / ml are considered to be protective (1). Studies have described that using levels of 1.3 µg / ml, up to 30% of the healthy population meets SAD criteria, in this particular study they used two techniques of Antibody measurement and theSSSSSSSSSy proposed that using the P5 of each serotype, which is usually less than 1 µg / ml, could be more appropriate for the diagnosis of SAD (6). However, the guidelines still consider 1.3 µg / ml as protective in a certain percentage of serotypes for disease definition.

Currently some centers abroad use Luminex for the determination of pneumococcal antibodies, a technique that is characterized by the detection of multiple proteins in it (1). This technique has some advantages compared to ELISA as: requirement of smaller samples, simultaneously performs the 23 serotypes and of lower cost, however, within the difficulties is that each center must define its ranges even when the correlation with ELISA is not perfect. (1)

DIAGNOSIS OF SPECIFIC ANTIBODY DEFICIENCY

The diagnosis of SAD is made in patients older than 2 with normal immunoglobulin counts, which do not have a response to a polysaccharide vaccine 4 weeks after administration. Normal levels of IgG and subclasses of IgG should be found.

Before making the diagnosis of SAD we must define what is considered as a normal response to the polysaccharide vaccine. For this it is necessary to be clear about the following factors (1):

1.- It is considered an adequate response to polysaccharide vaccine increase in titer above 1.3 µg / ml.

2.- If the patient has a pneumococcal antibody test prior to vaccination, it is considered that he had a vaccine response when he doubled the antibody titer for the specific serotype. If the titers were very high in the first exam, they should not be considered in the subsequent analysis.

3.- According to age, different percentages of antibodies in protective level must be considered in order to determine an adequate response. If the patient is older than 6, it is considered as an appropriate response, that he presents at least 70% of the serotypes studied at protective levels and if the patient is under 6 years of age he must have at least 50% of the serotypes in protective level.

Considering the normal ranges of response to the polysaccharide vaccine we can make the diagnosis of SAD; however we must consider another factor in patients who have received pneumococcal conjugate vaccine. In these patients, measurement of pneumococcal antibodies should be requested prior to vaccination with pneumococcal polysaccharide vaccine, to ensure that only T-independent response is being evaluated after the vaccine. It is possible to find several of the serotypes included in the polysaccharide vaccine within the correlates of protection but, this does not rule out that the patient has SAD, since post vaccine we seek to evaluate the T-independent response. For this, it is useful to consider the serotypes not included in the pneumococcal conjugate vaccine (Table 1). Single measurement after vaccination with polysaccharide vaccine could be considered in patients who have not received vaccination with pneumococcal conjugate, but in patients receiving conjugate vaccination, pre and post vaccination measurements should be performed to assess the increase in antibody titer. However, in our country it is often performed only post vaccination due to the high cost of the exam.

Considering the above elements, it is possible to define different criteria for diagnosis and severity depending on the patient's age. Two groups are defined: those under 6 and those over 6 years in age and for each age group, mild, moderate and severe deficiency is defined (less than two serotypes in protective titer). A group is also defined with memory phenotypes of deficient response (Table 2) (1-7).

n a patient who presents an adequate response after vaccination with pneumococcal polysaccharide, specific levels of pneumococcal antibodies should be measured again 6 months after vaccination, since there is a group of patients who respond transiently to the vaccine and then the correlates of protection fall again, this translates in memory phenotypes of deficient response for the development of these antibodies. Antibody control should be considered in patients who begin again with invasive infectious conditions before 6 months.

It is necessary to keep in mind that the request for the measurement of pneumococcal antibodies is also made in patients with suspicion of other immunodeficiencies, since the measurement of these antibodies provides information about the functional state of our immune system, which is necessary in the evaluation of primary immunodeficiencies such as: common variable immunodeficiency, hypogammaglobulinemia, ataxia telangiectasia, among others (8).

FOLLOW-UP AND MANAGEMENT OF PATIENTS WITH SPECIFIC ANTIBODY DEFICIENCY

For the management of patients with SAD, 3 therapeutic strategies have been defined: vaccination with pneumococcal conjugate vaccine in those patients who have not received it, antibiotic prophylaxis and monthly gamma globulin use. These 3 strategies can be used in combination or increased in stages according to the evolution of the patient.

The most validated strategy for these patients is the use of antibiotic prophylaxis with amoxicillin, azithromycin or cotrimoxazole (9-10-). Patients, depending on the clinic, may permanently require antibiotic prophylaxis for at least one year, considering the use of antibiotics for a shorter period, depending on the temporality of the symptoms, since there are patients who only present infectious conditions in the period of autumn-winter when the most acute respiratory infections occur. Pneumococcal conjugate vaccination is performed in patients who have not previously received this vaccination and a dose can be administered in patients who have received a complete dose at one year of life, this measure is related to the fact that the immunogenicity of the vaccine helps to protect the patient of invasive pneumococcal infections and helps maintain immune memory. The vaccine should be administered 8 weeks after vaccination with the pneumococcal polysaccharide vaccine. Revaccination with polysaccharide should be performed 5 years after the first dose is administered (7).

Table 2. Severity of specific antibody deficiency.

Phenotype*	Response to polysaccharide vaccine	
	Under 6 years old	**Over 6 years old**
Mild	With response in more than 50% of serotypes	With response in more than 70% of serotypes
Moderate	Less than 50% of serotypes are protective	Less than 70% of serotypes are protective
Severe	≤ 2 protective titer	≤ 2 protective titer
Memory deficient response	Adequate response loss 6 months post vaccination.* *	Adequate response loss 6 months post vaccination.* *

* Everyone should have a history of recurrent infections
** Loss of response is considered when it presents less than 50% of serotypes with protective antibody titer for those under 6 years and less than 70% of serotypes with protective antibody titer for those over 6. (8)

In patients with poor evolution, who despite adequate antibiotic prophylaxis and adequate administration of their vaccinations continue with rhino-sinus infectious conditions, recurrent acute otitis media, pneumonia or other types of invasive infections, use of gamma globulin in supplementation dose is recommended. It can be administered monthly intravenously (400-600 mg / kg every 3-4 weeks) or weekly subcutaneously 100mg / kg. The use of gamma globulin has not been studied prospectively in patients with this disease, but in different series with retrospective evaluation it has shown a decrease in the number of infections (9).

In addition to specific management, we must consider the management of other factors that may contribute to bacterial superinfection: optimize asthma management, allergic rhinitis and chronic sinusitis, early use of antibiotics if there is suspicion of possible infection and evaluate environmental factors such as smoking and assistance to preschool (1-6).

It is not yet possible to determine which are the patients that are going to recover from SAD, in the different series patients reported with spontaneous resolution, in which their immune system has matured and begins to present a response to polysaccharide antigens. This is related to the difference that can occur in the development of the T-independent immune response, since some patients may have a very early response to this type of antigen before two years of life and others may require more years to develop it (2). It has also been observed that the response depends on the pneumococcal serotype involved, with some serotypes responding earlier than others. A series described in Finland shows that of the 8 patients undergoing diagnosis diagnosed with SAD, five had a good response to a vaccine over a period of 3.8 years of follow-up, period in which they received a dose of pneumococcal vaccine again (4). On the contrary there are patients who require management with antibiotic prophylaxis for many years and an eventual monthly gamma globulin requirement (2).

CONCLUSION

It is relevant to consider in the study of patients with recurrent respiratory diseases, mainly acute otitis media, recurrent sinusitis and recurrent pneumonia, the diagnosis of SAD. Therefore, the study of specific antibodies must be carried out before and after four weeks of vaccination with a polysaccharide vaccine in children older than two.

A specific antibody deficit can be resolved with the maturity of the immune system while there are patients who require prolonged treatment with antibiotic prophylaxis and gamma globulin.

In Chile, it is necessary to increase the number of serotypes studied in the test in order to fully assess the response to the Pneumococcal polysaccharide vaccine, for the moment we can study 13 serotypes that guide us to diagnosis, so it is always necessary to correlate with each patient's clinical picture.

REFERENCES

1. Sorensen RU, Edgar D. Specific Antibody Deficiencies in Clinical Practice. J Allergy Clin Immunol Pract 2019;7:801-8.
2. Sorensen RU, Leiva LE, Javier FC III et al. Influence of age on the response to Sterptococcus pneumonia vaccine in patients with recurrent infections and normal immunoglobulin concentrations. J Allergy Clin Immunol 1998; 102:215-21.
3. Bossuyt X, Borgers H, Moens L, Verbinnnen B, Meyts

I. Age-dependent antibody response to pneumococcal polysaccharides. J Allergy Clin Immunol 2011; 127:1079-80.
4. Ruuskanen O, Nurkka A, Helminen M, Viljanen M.K, Käythy H, Kainulainen L, Specific Antibody Deficiency in children with recurrent respiratory infections: a contrlled study with fllow-up. Clinical and experimental Immunology, 172:238-244.
5. Oliveira et al Specific antibody deficiency in children with recurrent respiratory infections: a controlled study with follow-up. J Allergy Clin Immunol 2010;125:S297-305
6. Schaballie H, Bosh B, Schrijvers R, Proesmans M, De Boeck K, et al. Fifth Percentile Cutoff Values for Antipneumococcal Polysacharide and Anti-Salmonella typhi Vi IgG Describe a Normal Plysaccharide Response. Frontiers in Immunology May 2017;8:546.
7. Perez E, Bonilla FA, Orange JS, Ballow M, Specific Antobody Deficiency: Controversies in Diagnosis and Management. Frontiers in Immunology, May 2017 8; 586(8) Bonilla FA, Khan DA, Ballas Z, et all. Practice pararameter for diagnosis and management of primary immunedeficiency. J Allergy Clin Immunol 2015;136:1186-205
8. Fried A., Bonilla FA. Pathogenesis Diagnosis and Management of Primary Antibody Deficiency and Infections. Clin Microbiol Rev 2009 22;3:396-414
9. Edgar J, Richter A, Huisson A, Kumararatne D, Baxendale H, Bethune C, et al. Prescribing Immunoglobulin replacement therapy for patient with non.-clasical and secondary antibody deficiency: an analysis of the practice of clinical immunologist in the UK and Republic of Ireland. J Clin Immunol2018;38:2014-13