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Selective Antibody Deficiency and its Relation to the IgG2 and IgG3 Subclass Titers in Recurrent Respiratory Infections

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ABSTRACT

Background: Selective antibody deficiency with normal immunoglobulins (SADNI) may be identified as part of distinct primary or secondary immunodeficiency disorders. The clinical manifestations include recurrent, often severe or prolonged, upper or lower respiratory tract infections. **Objectives:** To evaluate SADNI in patients with recurrent sinopulmonary infections and its relation to IgG subclass deficiencies. **Methods:** In a case-control study, anti-pneumococcal antibody titer and IgG2, IgG3 levels before injection of pneumococcal vaccine and anti-pneumococcal antibody titer at least 4 weeks the vaccination were measured in 46 patients and 54 controls. The results were compared using student's *t-test*. **Results:** There was a significant correlation between age and anti-pneumococcal antibody titers before and after vaccination in patients. No significant relation was found between pre and post vaccination pneumococcal antibody titer and IgG2 and IgG3 in cases and controls ($p>0.05$). The mean of anti-pneumococcal antibody before and after vaccination were significantly different in cases and controls and were higher in control group ($p=0.01$, $p=0.001$, respectively). Anti-pneumococcal antibody titers in 97.8% of cases and 100% of controls group were normal (>3.4 µg/ml). 34.8% of cases and 9.1% of controls had low titers of anti-pneumococcal antibody (<20 µg/ml) while 18.7% of cases and no controls failed to respond to vaccine. **Conclusion:** Evaluation of anti-pneumococcal antibody titer in patients with recurrent, chronic and severe respiratory infections with normal immunoglobulin levels seems to be necessary as early diagnosis. Treatment of such a cases could prevent later sequelae such as mastoiditis and bronchiecstasia.

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Keywords: Streptococcus Pneumoniae, Respiratory Tract Infection, Antibody Deficiency

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INTRODUCTION

Humoral immune deficiency is the most common disorder of primary and secondary immunodeficiency diseases. Antibodies have a substantial role in protecting against infections and antibody deficiencies characteristically lead to recurrent, often severe upper and lower respiratory tract infections with encapsulated bacteria (e.g. *Streptococcus pneumonia* and *Heamophilus influenza*) (1).

In patients with suspected primary humoral immune deficiency quantitative immunoglobulin levels and specific antibody titers should be assessed. Selective antibody deficiency with normal or near normal serum immunoglobulin concentrations *(SADNI)* is a deficient specific antibody response to polysaccharide antigens (1,2). It can be seen in both children and adults with normal immunoglobulin and IgG subclass concentrations. This pathologic syndrome thus resembles the developmental status of human newborns and infants who readily produce antibodies against protein vaccines, but fail to respond to most polysaccharide vaccines until approximately two years of age. However, this syndrome can be diagnosed only in patients older than two years of age (3-5).

SADNI is also found in association with many primary and secondary immunodeficiencies. IgG2 subclass deficient patients have antibody responses to a restricted number of polysaccharides in the PPV vaccine. Frequently, these patients also have poor immunological memory, with IgG antibody titers decreasing to pre-immunization levels within 6 to 12 months (6).

Immunization with a polysaccharide pneumococcal vaccine is used to assess immunologic response to polysaccharide antigens in patients over two years of age. It has been recommended that the same laboratory perform the vaccination titers because different laboratories may measure titers to different serotypes. Children aged two to five years should generate protective titers for 50 percent of serotypes administered, and patients aged six and older, to more than 70 percent of serotypes (7-10).

In addition to providing diagnostic information, vaccination enhances immunity to a common respiratory pathogen in patients suffering from recurrent infections, at least in those who are able to respond (8). With the widespread use of the polysaccharide pneumococcal vaccine to assess immune function, this syndrome has become the most frequently identified immunodeficiency in clinics that evaluate patients with recurrent and/or severe infections (approximately 23 percent in one study) (11-12). Antibodies to bacterial polysaccharides are found predominantly IgG2 subclass. Accordingly, there are several associations between IgG2 subclass deficiencies and polysaccharide non-responders (3). Selective deficiency of antibodies to protein antigens rarely occurs in isolation and is usually part of a more profound defect in antibody production, such as common variable immunodeficiency, ataxia telangiectasia and hyper immunoglobulin M syndromes (1).

In the current study we evaluated anti-pneumococcal antibody titer pre and post vaccination, as well as IgG2 and IgG3 subclasses serum levels and its relation to anti-pneumococcal antibody levels in patients with recurrent sinopulmonary infections and controls pre and post pneumococcal vaccine.

MATERIALS AND METHODS

Using a non-randomized method, 46 SADNI cases over 18 years with chronic, recurrent or severe respiratory infections (sinusitis, otitis media, pneumonia, bronchiectasis) and other complicated infections (mastoiditis, osteomyelitis, etc.) that were referred to Alzahra University Hospital Immunology and Allergy Clinics and 54 controls from healthy subjects without recurrent infections with matching age and sex were entered to the study. Anti-pneumococcal antibodies titers and IgG2 and IgG3 levels were measured by enzyme linked immunosorbent assay (Binding site ELISA kits, UK). Pneumoccocal vaccine (Pneumovax^{23} Merck) was injected to all cases and controls and anti-pneumococcal antibody was measured at least four weeks after vaccination. The cut off values lower than <3.4 µg/ml were considered as deficient. Minimum detectable concentration of the ELISA assay was 0.01 µg/ml. Statistical analysis was done by SPSS software (Version 19, 2010, SPSS Inc, Chicago, IL, USA). Descriptive statistics of demographic variables (Means, Standard Deviation) and *t-test* (comparing the means of titers in 2 groups) were performed.

RESULTS

Hundred participants (46 cases and 54 controls) were enrolled in the study. Cases and controls were matched regarding age and sex. The mean ages of patients and controls were 16 ± 12 and 21 ± 13 years, respectively. 47.8% of cases and 55.6% of controls were men. There was a significant correlation between age and anti-pneumococcal antibody before and after vaccination in cases (p=0.005) and controls (p=0.009), and between age and IgG2 subclass levels in controls (p=0.001).

Table 1. Anti-pneumococcal antibody titers pre and post vaccination, and IgG2-IgG3 levels (mIU/ml).

Anti-pneumococcal antibody	Minimum		Maximum		Mean		P Value	
	Case	Control	Case	Control	Case	Control	Case	Control
Pre vaccination	2	11	423	833	70 ± 90	31.5 ± 137	0.005	0.001
Post vaccination	5	51	582	806	239 ± 157	348 ± 171	0.009	> 0.05
IgG2	26	235	12105	8427	297 ± 2308	3042 ± 1828	> 0.05	> 0.05
IgG3	68	190	3050	5508	654 ± 593	942 ± 97	> 0.05	> 0.05

The mean anti-pneumococcal antibody titer before and after vaccination were significantly different in cases (p=0.01) and controls (p=0.001) and both were higher in control group. No significant relationship was found between pre and post vaccination anti-pneumococcal antibody titer with IgG2 and IgG3 levels in cases and controls (p>0.05). Anti-Pneumococcal antibody titers in 45 (97.8%) of cases and 54 (100%) of controls were normal (>3.4 μg/ml). But the difference between these two group was not statistically significant (p>0.05). The patients who had low level of anti-pneumococcal antibody and their antipneumoccal levels increased four times after vaccination were considered as responders. 34.8% of cases had low titers of anti-pneumococcal antibody (<20μg/ml) and interestingly 18.7% of them did not respond to vaccine, but 1.9% of controls had low titer of antibody and all had responded to vaccine (Table 1).

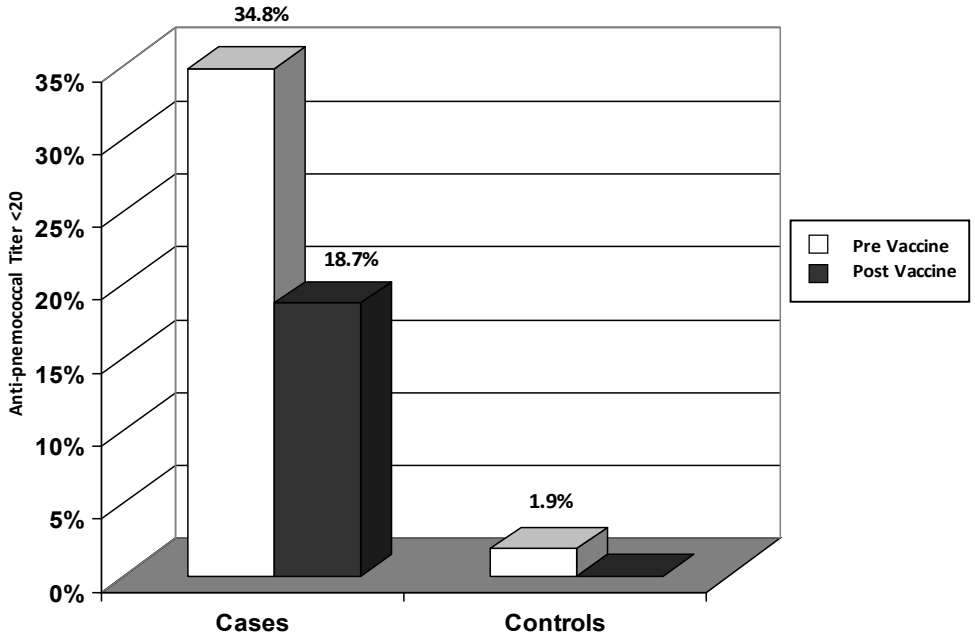

Figure 1. Response to vaccine in cases and controls.

DISCUSSION

Humoral immune deficiency refers to diseases resulting from impaired antibody production because of either a molecular defect intrinsic to B cells or a failure of interactions between B and T cells. Specific unresponsiveness to polysaccharide antigens is not unusualin children older than 2 years of age referred for evaluation of recurrent infections. IgG subclass deficiency is defined as a significant decrease in the levels of one or more subclasses of IgG in a patient whose total IgG concentration is normal. It is a laboratory finding that is not necessarily equal to a clinical disorder, and up to 20 percent of the population may have subnormal levels of one or more subclasses (3).

Several studies conducted in patients with long term recurrent and chronic respiratory infections referring to clinical Immunology and pediatric infectious clinics, have shown that reduction of IgG2 level causes bacterial infections such as *streptococcus pneumo-*

niae and *Haemophilus influenza* and IgG subclass deficiency causes decrease of immunoresponse to polysaccharide vaccines (1-3).

In patients with SADNI, the only abnormality is seen in the response to polysaccharide vaccines (5). Evaluation for SADNI involves the measurement of serum levels of IgG, IgA, IgM, IgG subclass levels and assessment of response to polysaccharide and (sometimes) protein vaccines (13). Immunologists debate the need for concomitant measurement of IgG subclasses in polysaccharide non-responders and differences of opinion exist. But it seems important to measure IgG subclasses because of the specific antibody abnormalities that are consistently found in association with IgG2 deficiency and patients with these findings should be categorized as having IgG2 subclass deficiency (14-15). Pneumococcal titers can be obtained in adults and children (older than two years) who either experienced natural pneumococcal infection, or received a polysaccharide vaccine in the past (14). Immunization with a polysaccharide pneumococcal vaccine (e.g., Pneumovax^{23}, Merck) to assess immunologic response to polysaccharide antigens in patients over two years of age. It is recommended to measure titers to 14 specific serotypes before vaccination, and at least four weeks after vaccination. In this study, significant association was found between age and anti-pnemococcal titer in both groups. Also association between IgG2 and age was significant in controls. A study in U.S.A which was done on 1000 patients with recurrent and chronic infections has reported that a pneumococcal serotype-specific IgG concentration ≥1.3 micrograms/mL is considered protective in all age groups, as these levels have been shown to be associated with protection against infection and colonization. It should be noted that the concentrations >1.3 micrograms/mL are associated with immunocompetence and protection against invasive and mucosal infections (7-8). Our finding showed anti-Pneumococcal antibody titer in 97.8% of cases and 100% of controls were normal (>3.4 μg/ml) and difference between these two groups was not statistically significant ($p>0.05$). Patients with low level of anti-pneumococcal antibody, whose antibody titer increases at least 4 fold after vaccination, are considered as responder. 34.8% of cases with a history of recurrent and chronic respiratory infections had low pneumococcal antibody titers (<20 μg/ml). 18.7% did not respond to the pneumococcal vaccine but in control group 1.9% of patients had low antibody titers who had responded to the vaccine. Other studies have reported that risk of respiratory infections increase in patients who have deficiency in response to polysaccharide antigens because of their weakened immune system and underlining diseases.

Our result indicated that the mean of anti-pneumococcal antibody before and after vaccination were significantly different in both group and were higher in control group (7). No relationship was found between anti-pneumococcal antibody and IgG2 and IgG3 levels in case and control group. More accurate determination of protective titers for specific serotypes due to variation in antibody properties in different serotypes and different age groups must be performed (14-15).

In conclusion evaluation of anti-pneumococcal antibody titer in patients with recurrent, chronic and severe respiratory infections with normal immunoglobulins level seems to be necessary and early diagnosis could prevent the later sequelae such as chronic sinopulmonary infection, mastoiditis and bronchiecstasia.

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