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Response to Polysaccharide Vaccination amongst Pediatric Patients with Common Variable Immunodeficiency Correlates with Clinical Disease

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ABSTRACT

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders, characterized by hypogammaglobulinemia and increased susceptibility to recurrent infections, autoimmunity and malignancies. We have previously shown that some pediatric patients with CVID can respond to meningococcal polysaccharide vaccine. Twelve pediatric cases with CVID were re-evaluated to determine whether bactericidal antibody responses or IgM memory B-cells correlate with the severity of disease resulting from the deficiency. We found that bronchiectasis and clinical manifestations of autoimmunity occur more commonly amongst non-responders to vaccine. In contrast, low populations of memory B-cells do not correlate with these sequelae. The results of this study could help pediatricians plan strategies for prevention of sequelae in children presenting with CVID.

Key words: Antibody response; common variable immunodeficiency; pediatrics

INTRODUCTION

Common variable immunodeficiency (CVID) is a heterogeneous group of primary immunodeficiency diseases, characterized by decreased serum levels of immunoglobulins in the absence of any recognized genetic abnormality.[1-3] Recurrent infections, autoimmune diseases, and malignancies are the most common manifestations in this group of patients.[1-5] Although defects of B-cell differentiation and several T-cell abnormalities have been reported in CVID,[5] the precise pathogenesis and genetic mechanism remains unknown.

It has recently been shown that some patients with CVID can produce protective post-vaccination titers and some cannot.[6-8] It has also been shown that some patients with CVID have low populations of IgM memory B-cells.[9-14] While severe clinical sequelae in some CVID patients with loss of memory B-cells have been reported,[10,13] this has not been investigated in children. Therefore, we evaluated the association between memory B-cell population size and antibody responses to polysaccharide vaccination with clinical disease in children with CVID.

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PATIENTS AND METHODS

Twelve CVID patients (8 male and 4 female), with mean age of 13.25±3.54 years, were evaluated in this study. In 9 families, parents were consanguine. The patients were referred to the main referral center for primary immunodeficiency diseases in Iran and are

under regular follow-up in this center at the Children's Medical Center Hospital, Tehran. The median age of patients at the time of diagnosis was 77.5 months (29 months-12 years), with a median diagnosis delay of 44 months (2-136 months). The diagnosis of CVID was made according to standard criteria, including decreased serum levels of at least two immunoglobulin isotypes and genetic exclusion of other antibody deficiencies associated with well-defined single gene defects.

All subjects were vaccinated with meningococcal polysaccharide vaccine, and the serum bactericidal antibody (SBA) assay was performed to measure antibody response titers before and three weeks after vaccination. The method of SBA assay was previously been described, in details.[6,7] Blood sampling in CVID patients was performed at least three weeks after immunoglobulin replacement therapy. Geometric mean titers (GMTs) were calculated and a SBA titer of ≥8 following vaccination and rise of ≥4-fold from pre- to post-vaccination was considered positive (responder patients). Non-responders were identified by having SBA titers of <8 post vaccination and a rise of <4-fold from pre- to post-vaccination.[6,7]

The results of pediatric CVID patients were re-evaluated considering the percentages of IgM memory B-cells and switched memory B-cells, which were measured by flow cytometry after isolation of peripheral blood mononuclear cells.[11] The patients were classified into three groups according to percentage of memory B-cells and switched memory B-cells; Ia: decreased switched memory B cells (IgM-IgD-CD27+ less than 0.4%) and increased CD21- B-cells (more than 20%), Ib: decreased switched memory B cells (less than 0.4%) and normal CD21- B-cells (less than 20%), and II: switched memory B cells more than 0.4%.[10,11]

RESULTS

Seven of 12 patients with CVID had a protective SBA titer post vaccination, but 5 patients did not produce protective titers. Serum bactericidal GMTs post-vaccination and also fold-rise in the responder group were significantly higher than non-responder group (P=0.003). With regard to memory B-cells and switched memory B-cells, 8 patients were in class I (2 Ia and 6 Ib) and 4 in class II. There was no association between the classification based on memory B-cell population and antibody response to polysaccharide vaccine (p=0.42). Two cases in class Ia were in the responder group. Three from class Ib were in the responder group, while another 3 cases from Ib were in the non-responder group. Additionally 2 cases from class II were in the responder group, while another 2 cases from class II were in non-responder group. We found no significant association between low switched memory B cells and the presence of bronchiectasis and autoimmune diseases. Although three of 8 from class I developed bronchiectasis, one of 4 from class II also had bronchiectasis (p=0.59). Three cases from class I had autoimmune disease, while 2 cases from class II had such manifestations as well (p=0.57). However, there was a significant association between the presence of bronchiectasis and autoimmune disease and poor antibody response to polysaccharide vaccine. None of the patients in the responder group developed bronchiectasis, while 4 of 5 cases in the non-responder group had bronchiectasis (p=0.01). Moreover 4 non-responders had autoimmune disease, whereas only 1 responder had autoimmune disease (p=0.04). The age of onset, the age at diagnosis, the diagnostic lag and the duration of disease were not associated with response to the polysaccharide vaccine (Table 1).

DISCUSSION

The wide variety of characteristics in CVID could be due to heterogeneity of underlying mechanisms.[1-3,5] The PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies) diagnostic criteria, which was established in the year 1999, introduced onset of hypogammaglobulinemia after 2 years of age and absent isohemagglutinins and/or poor response to vaccines as criteria for the diagnosis of CVID.[15] Meanwhile considering the reports on pediatric CVID,[1,3,16] in which many patients experienced their first infections after losing maternal immunoglobulin at 6 months,[1] it seems that the limitation of two years should be considered just for the age at diagnosis rather than the age at onset of disease manifestations. In fact, it is necessary to consider the diagnosis of CVID in patients older than 2 years of age, or even 4 years at the time of diagnosis (C. Cunningham-Rundles - pers. Communication), due to the possible transient hypogammaglobulinaemia. However, what would be the diagnosis of hypogammaglobulinemic patients who is found to have such immunodeficiency such immunodeficiency much earlier and continue to have it after that time?

Table 1. Characteristics of children with CVID who do not respond to polysaccharide vaccine.

Characteristics	Responders (n=7)	Non-responders (n=5)	P-value
Age: mean±SD			
Current age (years)	13.3±3.8	13.2±3.6	0.40
Onset age (months)	26.3±24.9	23.6±33.7	0.35
Diagnosis age (months)	98.7±38.6	54.2±39.8	0.35
Diagnosis delay (months)	72.4±40.6	30.6±18.2	0.36
Duration of disease (months)	133.1±48.3	134.8±56.3	0.36
Serum Immunoglobulin level: mean±SD			
IgG (mg/dl)	335.9±141.2	290.0±58.3	0.36
IgM (mg/dl)	22.1±13.2	40.6±28.0	0.35
IgA (mg/dl)	10.4±9.6	9.4±10.5	0.29
B-cells subpopulations: median, range			
%IgD- CD27+ of peripheral blood lymphocytes	0.18 (0.13-0.98)	0.21 (0.17-1.44)	0.36
%CD21- of CD19+ B-lymphocytes	8.0 (4.88-61.34)	7.5 (4.78-14.27)	0.36
Serum bactericidal geometric mean titers			
GMTs post-vaccination	19.5	1.32	0.003
GMTs fold rise	9.75	1.14	0.003
Clinical disease: number, percent			
Bronchiectasis	0	4 (80%)	0.01
Autoimmunity	1 (14.3%)	4 (80%)	0.04

Indeed while poor antibody response to vaccines was considered as a criterion for the diagnosis of CVID, the presence of antibodies against protein or polysaccharide antigens was reported in a group of patients with CVID.[3, 6-8] While evaluation of antibody response is not diriment due to the limited number of tested antigens, it is not clear how many antigens we have to test and which conclusion could be drawn in the cases with normal response to some antigens and a defective antibody response to others (A. Plebani - pers. communication). In a recent study on CVID patients whom immunized with some anti-peptide and anti-polysaccharide vaccines, positive vaccination responses was detected in 23% against polypeptide vaccines and in 18% against polysaccharide antigens; consequently they concluded that positive vaccination responses cannot exclude the diagnosis of CVID.[8] Some experts in this field believe that the lack of antibody and poor vaccine responses are essential for CVID diagnosis (C. Cunningham-Rundles - pers. communication). If so, a distinct group of patients with predominantly antibody deficiencies with severe reduction in serum IgG and IgA and normal vaccination responses (at least to some antigens) could be considered in IUIS (International Union of Immunological Societies) classification.[17] Nevertheless, it is obviously a controversial field, which depends on definition of CVID; following a classification along the lines hypogammaglobulinemia and CVID as a subgroup defined by poor vaccination response or CVID as a subgroup of hypogammaglobulinemia defined by the exculsion of others independent from vaccination response (K. Warnatz - pers. communication).

Considering high frequency of consanguinity in our CVID patients,[18] especially in pediatrics cases, and our previous finding on positive relation between consanguinity and radiosensitivity,[19] an autosomal recessive genetic defect could be supposed in pediatric CVID patients, which definitely needs further investigation in this regard.

In this study, we also re-evaluated the role of switched memory B-cells in development of disease sequelae amongst a paediatric population. Although we found no association in contrast to previous reports in adults,[9,12] a significant association was found between poor antibody response to polysaccharide vaccines and bronchiectasis and autoimmunity. The development of bronchiectasis in the non-responder group may reflect the severity of the immune defect. Although several attempts have recently been made to classify CVID on the basis of memory B-cells,[9-14] it is not clear whether such classification could be clinically useful in children. Although decreased memory B-cells and poor antibody response to polysaccharide antigens have been denoted class I of CVID,[9] this may not compatible in children.

Thus, considering the results of this study and the previous study,[9] it could be suggested that while low IgM memory B-cells may be detected in CVID patients with recurrent pneumonia and bronchiectasis, this fact could be true in the cases who have an associated poor antibody response to polysaccharide antigens. This could underlie recurrent bacterial pneumonia and consequent bronchiectasis in this group of patients.[9] In contrast, good antibody responses to polysaccharide antigens could protect CVID patients from bacterial pneumonia and consequently bronchiectasis. The responder patients may have a good prognosis, while non-responders may develop complications such as bronchiectasis and autoimmunity. Therefore, measurement of the antibody response to polysaccharide antigens, a simple and practical tool, could be conducted at the time of diagnosis of children with CVID. However, we should emphasize that the sample size of our study was small and consequently the statistical power of the study was low. If the results of this study be confirmed elsewhere, it would help physicians plan strategies for prevention of sequelae in children presenting with CVID.

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