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Antigen-specific IgA titres after 23-valent pneumococcal vaccine indicate transient antibody deficiency disease in children

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ABSTRACT

Paediatric patients with antibody deficiency may either be delayed in development of humoral immunity or may be persistently deficient in antibody production. To differentiate between these entities, we examined the 23-valent pneumococcal polysaccharide (PnPS) vaccine-induced IgM-, IgG- and IgA antibody responses in a cohort of 66 children with recurrent respiratory tract infections. Individual serum titres against 11 pneumococcal serotypes were measured by Luminex. The cohort contained 33 antibody deficiency patients, 17 transient antibody deficiency patients and 16 patients without antibody deficiency diagnosis (control group). Transient antibody deficiency patients produced consistently higher levels of PnPS-specific IgA responses than antibody deficiency patients. Decreased IgA responses to serotypes 1, 5, 7F and 18C were most discriminative to stratify transient antibody deficiency patients from antibody deficiency patients with persistent disease. We conclude that measuring PnPS-specific IgA responses may predict the disease course in young children diagnosed with antibody deficiency and suggest confirmation of these data in a prospective setting.

1. Introduction

Common Variable Immunodeficiency Disorder (CVID) is one of the most prevalent primary immunodeficiency in children and adults [1,2]. Diagnosis is based on a combination of decreased (<−2SD) serum IgG and IgA/IgM levels, absent isohemagglutinins and/or insufficient vaccination responses against tetanus and/or pneumococcal polysaccharide vaccines [3]. In paediatric patients, impaired immunoglobulin levels and defective responses against these vaccinations bring forward antibody-deficient children who may either be delayed in the development of the humoral branch of their immune system, or alternatively be persistently deficient in antibody production [4,5], predicting a life-long disease prospect which implicates more frequent and intense immune monitoring and additional prophylactic and therapeutic measures [6].

Recent studies indicate that the assessment of anti-PnPS IgA- and IgM responses can be of additional value in immunodeficiency diagnostics [7–12]. For example, adult CVID patients with low memory IgM B-cell percentages and combined insufficient anti-PnPS IgM- and IgA responses were described to be at increased risk of developing pulmonary complications such as bronchiectasis [8,11]. In the elderly, decreased anti-PnPS IgA- and IgM responses seem to be indicative for immunosenescence, more than the specific anti-PnPS IgG responses [9]. The anti-PnPS IgA response of elderly shows delayed maturation through which it only reaches an anti-PnPS IgA response level similar to that in young adults after 28 days.

In this study, we hypothesized that children diagnosed with antibody deficiency disease based on insufficient anti-PnPS IgG responses but with partially conserved anti-PnPS IgA- and IgM responses will display delayed maturation of the immune response with spontaneous recovery. We therefore investigated a cohort of 66 children with recurrent respiratory infections, and analyzed their vaccination-induced IgM-, IgG- and IgA anti-pneumococcal polysaccharide (PnPS) responses. We show that measuring

Abbreviations: APAD, anti-polysaccharide antibody deficiency; AUC, area under the curve; CVID, Common Variable Immunodeficiency Disorder; PnPS, pneumococcal polysaccharide; SD, standard deviation; TAD, transient antibody deficiency of childhood; ROC, receiver operating characteristic.

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PnPS-specific IgA responses may indicate the antibody deficiency disease course in young children, and provide cut-off values for PnPS serotypes 1, 5, 7F, 18C that may be of diagnostic use with 84% accuracy.

2. Methods

2.1. Subjects

We conducted a retrospective cohort study in 96 children (age range: 3–17 years) who underwent protocolled diagnostic- and follow up evaluations for suspected antibody deficiency at the Wilhelmina Children's Hospital/University Medical Centre Utrecht between 2008 and 2014. From the 96 patient records studied, 66 suspected antibody deficiency patients had a complete diagnostic and follow up (after 3–5 years) evaluation of laboratory and clinical values as specified below. These patients were included for analysis. For laboratory measurements initial samples were used, as obtained when the subjects were first seen at the patient outward clinic. Informed consent to analyze the data obtained from the medical charts was waived by the Institutional Review Board.

2.2. Laboratory measurements

The standardized diagnostic evaluation included a full blood count and differentiation, measurement of serum IgM, IgG and IgA titres, IgG subclass titres and measurement of anti-pneumococcal IgM, IgG and IgA antibodies 4–6 weeks after 23-valent pneumococcal polysaccharide (PnPS) vaccine (Pneumovax®, Merck, The Netherlands). Follow up evaluations included evaluation of IgM, IgG, IgG subclass and IgA levels and a repeat test of specific antibody responses to PnPS vaccine. Patient serum samples were stored pre- and 4–6 weeks post vaccination with 23-valent PnPS vaccine at −80 °C. Anti-PnPS IgM, IgG and IgA responses to pneumococcal serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F were determined by Luminex as described previously [13,14].

Criteria for a sufficient anti-PnPS IgG response were age dependent: in children <6 years, a normal response was defined as serotype specific IgG responses of >1 μg/ml in at least 6/11 (50%) of serotypes measured, in children >6 years a normal response was defined as IgG responses of >1 μg/ml in at least 8/11 (75%) of serotypes measured [15]. Four patients were pre-vaccinated with a 7-valent pneumococcal conjugate vaccine (PnC, Prevnar®, Pfizer, The Netherlands) and of these patients only PnPS serotypes 1, 3, 4 and 7F (which are not present in the 7-valent PnC vaccine) were analyzed.

2.3. Definition of patient groups

The 66 subjects were divided in the following three groups.

1. Antibody deficiency patients
   Patients diagnosed with CVID or anti-polysaccharide antibody deficiency (APAD) based on the following criteria.
   CVID: 1. recurrent infections (respiratory and/or gastrointestinal), 2. insufficient anti-PnPS IgG responses (see above), 3. IgG and IgA and/or IgM levels below −2SD, and 4. exclusion of known causes of hypogammaglobulinemia.
   APAD: 1. recurrent infections (respiratory and/or gastrointestinal), 2. insufficient anti-PnPS IgG responses (see above), and 3. normal values for IgG, IgA and IgM.
   All patients in the group of persistent antibody deficiency had no change in laboratory or clinical diagnosis after 3–5 years of follow up.

Table 1
Baseline characteristics.

	Patients	Control group
Number	50 (75%)	16 (25%)
Antibody deficiency patients	33 (75%)	
TAD patients	17 (25%)	
Age at vaccination response measurement (years, median)	8 (3–17)	10 (5–17)
TAD patients	6 (3–17)	
Antibody deficiency patients	9 (3–17)	
Gender (% male)	54%	31%
TAD patients	59%	
Antibody deficiency patients	52%	
Number of TAD patients per age group (n)		
3–6 years	8	
6–10 years	2	
10–17 years	7	

Baseline characteristics of patient- and control group. TAD, transient antibody deficiency.

2. Transient antibody deficiency of childhood (TAD)
   Patients with a diagnosis of transient antibody deficiency of childhood had an initial diagnosis of CVID or anti-polysaccharide antibody deficiency, however, they showed normalization of laboratory and clinical symptoms in the period 3–5 years following initial diagnosis. Because patients included in this study were >3 years old and had insufficient anti-PnPS IgG responses, they did not classify for diagnosis of transient hypogammaglobulinemia of the infancy (THI) [6,16].
3. Control group
   The control group consisted of subjects evaluated for recurrent infections and who proved to have normal levels of IgG, IgA and IgM, and intact vaccination responses, and thus did not fulfil criteria for antibody deficiency disease.

2.4. Statistical analysis

All statistical analyses were performed with SPSS 20.0 software for Windows (SPSS Inc., Chicago, IL, USA). To compare continuous data between two groups, Mann–Whitney *U* test was used for non-parametric data. Categorical data were tested with Pearson's chi-square tests. Receiver operator characteristics curves were composed through SPSS and area under the curves calculated. Tests were performed two-tailed, and p-values ≤ 0.05 were considered significant.

3. Results

We included 33 antibody deficiency disease patients, 17 were transient antibody deficiency patients and 16 patients who had no antibody deficiency diagnosis and served as control group onward (see Table 1). The median age of the antibody deficiency patients was 9 years, 6 years for TAD patients and 10 years for the control group. All patients had recurrent respiratory infections and one antibody deficiency patient developed bronchiectasis, there were no autoimmune manifestations in our patient group. Maturation of the humoral immune system of the TAD patients occurred up to 16 years of age (see Table 1). In our cohort IgG, IgA and IgM levels did not stratify antibody deficiency patients from transient antibody deficiency (TAD) patients. Also memory IgM, IgG and IgA B-cell percentages of CVID patients were not statistically different between both groups (Supplemental Table 2). Within the antibody deficiency patient group 45% was treated with immunoglobulin replacement therapy, in comparison to 30% temporarily in the transient antibody deficiency children group.

We first compared the anti-PnPS IgM, IgG and IgA responses of the whole antibody deficiency patient group ($n = 50$) to the control