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ORIGINAL ARTICLE

A comparison of B cell subsets in primary immune deficiencies that progress with antibody deficiency and age-matched healthy children

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Transient hypogammaglobulinaemia

Abstract
Background: The objective of this study was to examine the B lymphocyte subsets in primary immunodeficiency that progress with antibody deficiency.
Methods: The patients' naive, memory, class-switched memory and non-switched memory B cells were compared with those of healthy individuals of matching ages using flow cytometry.
Results: A total of 67 patients with antibody deficiency and 28 healthy children of matching ages were included in the study. The median age of the patients was six years (min–max: 1–24) and 40 (59.7%) were male. The median age of the healthy controls was again six years (min–max: 1–17) and 12 (42.8%) were male. Patients with common variable immunodeficiency had higher relative counts of naive cells when compared with the control group; however, they were found to have lower relative counts of memory, relative and absolute counts of non-switched and relative counts of switched B lymphocytes ($p = 0.001$, 0.023, 0.003–0.003, 0.001, respectively). In patients with selective IgA deficiency, similar to patients with common variable immunodeficiency, the relative counts of naive cells were found to be higher, while the relative counts of memory and relative and absolute counts of non-switched B lymphocytes were found to be lower when compared with the control group ($p = 0.011$, 0.032, 0.006–0.009, respectively). Although patients with selective IgM deficiency had higher relative counts of naive B cells when compared with the control group, they had lower relative and absolute counts of non-switched B lymphocytes ($p = 0.008$–0.016).
Conclusions: The B lymphocyte subsets of patients with selective IgA deficiency are largely similar to those of patients with common variable immunodeficiency. Both illness groups exhibit low levels of memory B cells.

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Introduction

The early stages of B cell development occur in the bone marrow. B cells then continue to mature in the peripheral lymphoid organs, where they encounter foreign antigens.[1] Antigenic stimulation triggers the proliferation and differentiation of antigen-specific cells. Successive steps in B cell differentiation result in the generation of two types of affinity-matured B cells: memory B cells and antibody-secreting plasma cells.[2,3] Memory B cells continuously circulate between the blood and lymphoid organs and can rapidly differentiate into effector cells following cognate antigen recognition. By contrast, long-living plasma cells can reside in the bone marrow and produce high-affinity antibodies without antigenic stimulation.[4–6]

Antibody deficiency is defined as a decrease of 2SD (two standard deviations) in the levels of at least one of the immunoglobulin (Ig) isotypes compared to the mean values of age.[7]. The objective of this study was to analyse the memory B cell subsets of patients with antibody deficiencies, such as partial IgA deficiency (pIgAD), selective IgA deficiency (sIgAD), selective IgM deficiency (sIgMD), common variable immunodeficiency (CVID), unclassified hypogammaglobinaemia (UCH), and transient hypogammaglobinaemia in infancy (THI).

Materials and methods

Study population

The study had a prospective design. Patients who were followed by our paediatric immunology and allergy department between March 2012 and March 2014 were included in the study. Out of the 67 patients with antibody deficiencies, 20 patients with THI, 18 patients with UCH, 13 patients with CVID, 7 patients with sIgAD, 5 patients with sIgMD, and 4 patients with pIgAD participated in the study. Twenty-eight healthy, age-matched children were included in the study as the control group. Sixty-seven patients with antibody deficiencies were grouped according to their diagnoses. Each patient group was compared with the children in the control group. On the condition that their ages matched, some children from the control group were used to compare data with more than one of the patient groups.

Definition of antibody deficiency

The patients' serum Ig levels were measured using nephelometry. Normal values were interpreted according to healthy, age-matched Turkish children, as reported by Tezcan et al.[8] Patients who used antiepileptics and corticosteroids, or who had antibody deficiencies that were caused by other chronic diseases, immunodeficiencies, and congenital anomalies, were excluded from the study.

Definition of primary immunodeficiencies

Transient hypogammaglobinaemia in infancy was diagnosed according to the following criteria:

- Low serum IgG levels that were accompanied by low IgA and/or IgM levels upon admission.
- Normalisation of low Ig levels during follow-up.
- Normal production of an antibody specific to isohaemagglutinins.
- Intact cellular immunity.

UCH was diagnosed according to the following criteria:

- Low serum IgG levels that were accompanied by low IgA and/or IgM levels upon admission.
- Low Ig levels by the end of follow-up.
- Normal production of an antibody specific to isohaemagglutinins.
- Intact cellular immunity.

Selective IgA deficiency is defined as IgA levels <7 mg/dL in children older than four years of age.

Partial IgA deficiency is defined in children who are older than four years of age as IgA levels <2SD of the age-matched normal values.

Selective IgM deficiency is defined as IgM levels <2SD of the age-matched normal values.

The criteria for the diagnoses of common variable immunodeficiencies included the presence of a low value of at least one of the IgM or IgA levels and all of what follows in male or female patients with IgG levels that were clearly low (average levels were lower than at least 2SD of age):

- Onset of immune deficiencies after the age of two.
- Absence of isohaemagglutinin and/or a weak immune response to vaccines.
- Exclusion of other factors that cause antibody deficiency.[7,9,10]

Laboratory studies

Total serum Ig levels were measured using commercially available nephelometry kits (Dade Behring Marburg GmbH, Marburg, Germany). For the antibody response, the patients' poliovirus responses and isohaemagglutinin levels were studied. Three cc of blood was taken from each patient and stored in tubes containing ethylenediamine tetraacetic acid (EDTA). Immunophenotyping was performed using the following monoclonal antibodies: IgD PE, CD19 APC, and CD27 FITC (BD Biosciences, Pharmingen, Germany). The percentages of the lymphocyte subsets in the CD19 complex were analysed using flow cytometry (BD FACS Calibur; BD Biosciences, San Jose, USA). The peripheral $CD19^+$ B cell subsets were defined as follows: memory B cells as $CD19^+CD27^+$, naive mature B cells as $CD19^+CD27^-IgD^+$, non-switched B cells as $CD19^+CD27^+IgD^+$, and class-switched memory B cells as $CD19^+CD27^+IgD^-$.[11]

Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Version 15, Windows). All data was expressed as the median or percentages that were caused by distributions that were not considered