

Decreased serum IgD level in patients with immunoglobulin A deficiency

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Abstract

Background: The role of circulating immunoglobulin D is still unclear. There are many data treating about serum IgD levels in different immunological diseases, but they give no answer for the question about the mechanisms of regulation of this isotype synthesis.

Methods: Serum of 18 IgA-deficient children was investigated to assess immunoglobulin D levels. As a controls, serum of 18 nonimmunodeficient females was used.

Results: There was a big disparity of serum IgD levels in the control group. Serum IgD levels in IgA-deficient children were found above 4 times below the levels observed in controls ($p < 0.05$). No correlation between serum IgD levels and the levels of IgM, IgG and the age in this group of patients was observed.

Conclusion: Decreased serum IgD levels in children with Immunoglobulin A-deficiency may suggest the existence of similar regulatory mechanism of these isotypes.

Key words: immunoglobulin D, IgA deficiency, primary immunodeficiency.

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Introduction

Immunoglobulin D was discovered in 1965. Since then many different functions of this isotype have been confirmed: a role in the maturation of B cell and antigen response, where serves as a membrane receptor [1, 2]. Much less is known about its function as a circulating IgD.

In spite of sparing of IgD-secreting plasma cells observed in the bone marrow, there is a positive correlation between its number and serum IgD level. In addition, individuals with high serum IgD level produce specific IgD antibodies after antigenic challenge [1, 3].

Some informations about the role of circulating IgD may be available from studies of immunopathological diseases. It is observed that in disorders with immune activation and immunodeficiencies, serum IgD level is associated with the concentration of other isotypes. Significant number of individuals have increased levels of IgD in such disorders as HIV infections, Down's syndrome, chronic bronchopulmonary aspergillosis, atopy, acute hepatitis,

salmonellosis, chronic obstructive pulmonary disease, tuberculosis, leprosy, malaria, hyper-IgE syndrome, Hodgkin's disease and in children following chemotherapy or after bone marrow transplantation. Significantly decreased serum IgD levels were observed in some immunodeficiencies: non-X-link agammaglobulinemia and IgA deficiency [1-3].

These observations imply, that a number of factors may be involved in the production and regulation of synthesis of circulating IgD.

According to previous studies, the aim of this work was to assess serum IgD levels in patients with isolated IgA deficiency.

Material and methods

Patients and controls

A total of 18 patients with selective IgA deficiency (10 males and 8 females) were included in this study. Mean

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age of the patients was 9.69 ± 3.55 (range 5-16). According to diagnostic criteria established by the European Society for Immunodeficiencies (ESID) [4], all patients had serum IgA levels below 0.07 g/l associated with normal serum levels of IgG and IgM, as was assessed by means of ELISA method (data not shown). Eight out of IgA-deficient patients had undetectable serum IgA levels.

The control group comprised 18 volunteers (females, mean age 22.13 ± 3.52) with no history of primary or secondary immunodeficiencies.

All individuals included in this study were healthy at time of collection of samples. None of them have been receiving any pharmaceuticals for at least 2 weeks before the sample collection. All individuals were Caucasians. This study was approved by the Bioethical Committee of the Medical University of Wrocław.

Serum samples

Venous blood samples were collected into vacuum blood collection tubes without additives. Blood was allowed to clot and next centrifuged at $450 \times g$ for 10 min. Serum samples were immediately frozen and stored at -70°C until measurement. All sera were frozen and thawed only once.

Measurement of serum IgD

Serum IgD levels were determined by single radial immunodiffusion using commercially available kit with agarose gel containing mono-specific antibody (The BINDARID™, The Binding Side). Sensitivity of the serum IgD determination was between 1.2-89.2 mg/l.

Statistical analysis

Comparison of serum IgD levels between two groups was performed using Mann-Whitney U-test, because of the

nongaussian distribution of the data. Correlation coefficient was performed by the Spearman rank test. A p -value $< 0,05$ was considered as significant.

Results

Serum IgD levels in patients and controls are depicted on the figure 1.

In this study variation in serum IgD level in control group was observed (range 3.78 – 82.7 mg/l). Mean serum IgD level in this group was 20.67 ± 23.61 mg/l. In IgA-deficient patients it was found above 4 times below the level observed in the controls (mean 5.02 ± 3.19 mg/l, range 0 – 13.3 mg/l). This difference proved statistically significant ($p < 0.05$). Undetectable serum IgD level (< 1.2 mg/l) was found only in one patient.

There was not any correlation of data with age and other class of immunoglobulin in every group studied.

Discussion

This results are in agreement with previous observations of decreased serum IgD level in patients with primary immunodeficiencies, including IgAD [3, 5-8]. On the other hand, some authors depict lack of significant differences in IgD levels in serum and secretions in IgAD patients and controls [9, 10]. Moreover, in hypogammaglobulinemic patients, serum IgD levels are usually normal or increased [5, 11]. This may suggest compensatory role of this isotype. Observations of Jankowski and Ziemiańska [12] indicating that increased serum IgD levels in IgD-deficient children are connected with better clinical condition of this patients and lower susceptibility to recurrent infections, seems to confirm above-mentioned results.

It was observed that serum IgD levels are proportional to other isotypes [2]. Our results did not prove any correlation between IgD levels and the levels of other isotypes in serum tested. This results are in contradiction with many data showing positive correlation between IgD serum levels and IgA or IgE in healthy individuals and patients suffering from some infectious diseases (hepatitis of B type, tuberculosis) [13-15], as well as in patients with primary immunodeficiency and HIV-infected persons [3, 16-18]. On the other hand, lack of association between serum IgD levels and the levels of other isotypes observed by us, is in agreement with previous findings by Litzman *et al.* [3], showing that circulating IgD levels do not always correlate with the serum levels of IgG and IgM [19].

We did not confirm the association between serum IgD levels with the age and sex in both groups included in this study. This may be a result of little differentiation of individuals included in each group. This lack of association is in agreement with previous findings of Dunette *et al.* [20]. This may suggest the association of serum IgD levels with some other factors. Litzman *et al.* [3] investigated the rela-

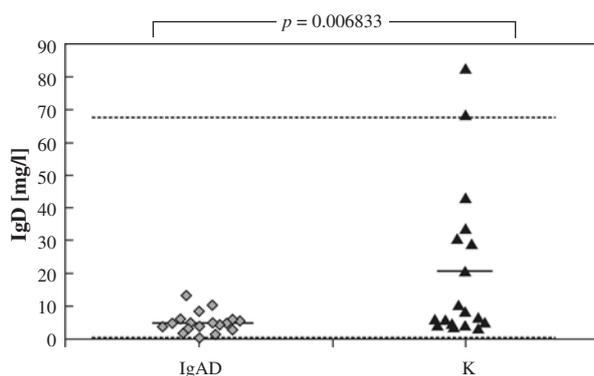


Fig. 1. Serum IgD levels in the group of IgA-deficient children and healthy controls

Points depicts serum IgD levels in every group studied. Horizontal lines depicts mean serum IgD level in each of the group. Intermittent line shows a group of 95.5 % all measurements in the control group (mean ± 2 standard deviations).

tionship between serum levels of this isotype and markers of activation of the immune system (erythrocyte sedimentation rate, leukocyte count, C-reactive protein level, the percentage of CD4+CD25+, CD8+CD25+, CD3+ and CD71+ lymphocytes and C3 complement component level). They observed a significant correlation of serum IgD levels only with leukocyte count and the percentage of CD4+CD25+ lymphocyte. This data indicate a minor association of serum IgD levels with the immune activation.

The results of this above mentioned studies suggest that IgD production may be influenced by some genetic factors. Previous findings of Calvo *et al.* [21] depict the association of isolated IgD deficiency (IgDD) with alleles of the human leukocyte antigens (HLA-B8 and DR3). Our observations confirm the association of this same alleles of HLA in the group of patients with IgA-deficiency included in this study [22]. The role of HLA-B8, DR3 in IgAD susceptibility was conformed also by Hammarström *et al.* [23], Heikkilä *et al.* [24] and Vořechovský *et al.* [25].

Decreased serum IgD levels in patient with IgA deficiency and the same genetic predisposition may suggest the existence of similar regulatory mechanisms of serum IgD and IgA production. This suggestions may confirm observations of Levan-Petit *et al.* [26]. In *in vitro* studies this group of researchers exerted that, in IgD synthesis regulation participate cytokines of the Th2 cells, this same as in IgA synthesis regulation (IL-4, IL-10). The existence of identical synthesis regulation mechanisms of this both isotypes is supported by the observation of increased level of IgA and IgD in recurrent infections [27] and in hyper-IgD syndrome (HIDS) [28].

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