Clinical and Immunological Studies in Patients with an Increased Serum IgD Level

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Increased levels of serum IgD can be found in single patients with a variety of clinical syndromes and in the disease entity designated hyper-IgD syndrome which is associated with periodic fever and lymphadenopathy. We investigated 17 patients, both children and adults, with high serum IgD levels ranging from 220 to 5300 IU/ml. Eight patients had periodic fever and lymphadenopathy, four showed a humoral immunodeficiency, and the remainder had a variety of clinical abnormalities. Serum IgA levels were consistently high in all patients except in those with an immunodeficiency. Serum IgD complexes were detectable in each serum, which indicates that the occurrence is not pathognomonic for the syndrome of periodic fever. Antibody formation against the primary antigen Helix pomatia hemocyanine and the secondary antigen tetanus toxoid showed no abnormalities in the patients without an immunodeficiency. Bone marrow origin of serum IgD was strongly suggested by enumeration of IgD-containing plasma cells. We conclude that no apparent relationship exists between the several clinical syndromes and increased serum IgD.

KEY WORDS: Serum IgD; periodic fever; immunodeficiency; immune status.

INTRODUCTION

The function of the human immunoglobulin isotype IgD, as identified in 1964 by Rowe and Fahey (1), is still not completely solved. The IgD molecule occurs as membrane-bound protein on lymphocytes of B-cell lineage and also in serum and other body fluids. Membrane-bound IgD probably plays a role in antigen-triggered B-lymphocyte differentiation (2, 3). Although antibody activity can be detected in soluble serum IgD, its role in the defense against infections is less clear since effector functions such as binding to phagocytes are lacking (4, 5).

IgD comprises about 1% of the total serum immunoglobulin pool in man. The concentration in serum as measured in healthy infants and adults is age dependent and shows a considerable biological variation within people of the same age (1, 6, 7). Serum IgD levels of a population are not normally distributed (7). Dunette et al. (8) showed in a study of 300 individuals aged 6 to 18 years that about 14% of the individuals had an extremely low serum IgD. The latter phenomenon appeared to be genetically determined, in that an autosomal recessive pattern of inheritance and an HLA association were described (8, 9). In contrast, a substantial number of healthy individuals showed an increased serum IgD level (1, 7, 8; unpublished observations of Out, Vossen, and Zegers), but a discernible inheritance pattern or HLA association was not demonstrable (8).

The role of serum IgD in disease is not clear. Increased serum IgD levels are found in patients with various types of immunodeficiency diseases, in patients with severe recurrent infections of the respiratory tract, and in single patients with a variety of clinical syndromes or abnormalities (10). Recently a clinical disease entity has been described, designated the hyper-IgD syndrome, which is characterized by periodic fever and lymphadenopathy associated with strongly increased levels of serum IgD of up to 6000 IU/ml serum (11).

Since we were interested in the role of serum IgD in disease a multicenter study was designed aimed...
to analyze the clinical and immunological findings in a series of patients with a variety of diagnoses and with high serum IgD levels which were under the care of the members of the Dutch Working Group for Immunodeficiencies. The main criterion for entry in the study was a level of serum IgD equal or higher than 150 IU/ml as determined on two occasions with an interval of at least 1 month.

PATIENTS AND METHODS

Patients were entered into this multicenter study after informed consent was obtained. The entry criterion was a serum IgD level higher than 150 IU/ml on two occasions at least 1 month apart. Included were 6 adults and 11 children; age varied between 3 and 60 years.

The data were collected according to a protocol written by the Dutch Working Group for Immunodeficiencies (see Table I).

With respect to the history of the patient and his/her family, special attention was paid to infectious diseases, recurrent fever, vaccination sequelae, allergic symptoms, malignancy, autoimmune diseases, tonsillectomy, adenotomy, and appendectomy.

White blood-cell count, total lymphocyte counts, routine urine analysis, serum autoantibodies such as antibodies against erythrocytes, antinuclear antibodies, anti-double-stranded DNA, rheumatoid factors, and serum immunoglobulin (Ig) levels were determined by standard methods.

### Table I. Protocol Design

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>0</th>
<th>14</th>
<th>21</th>
<th>35</th>
<th>63</th>
<th>120</th>
<th>240</th>
<th>360</th>
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<tbody>
<tr>
<td>Physical examination, routine laboratory&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Tetanus toxoid</td>
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<td>Tetanus toxoid antibodies</td>
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<td>HPH immunization</td>
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<tr>
<td>HPH antibodies</td>
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<td>x</td>
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<tr>
<td>Serum IgD levels</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Bone marrow</td>
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<tr>
<td>Cellular immunity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>x</td>
<td>x</td>
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</table>

<sup>a</sup>White blood-cell count, total lymphocyte count, routine analysis, serum autoantibodies, serum immunoglobulin levels, and saliva collection.

<sup>b</sup>Circulating B- and T-cell numbers and in vitro proliferative responses of lymphocytes to mitogens, antigens, and alloge neic cells.

Saliva was collected during 15 min according to Lourie (12). The first specimen was discarded; in the second specimen IgM, IgG, IgA, and IgD levels were measured (13, 14).

IgD complexes were determined by Dr. M. R. Daha (Leiden) in serum that had been immediately frozen at -70°C. After precipitation with polyethylene glycol 6000 (final concentration, 3.5%), high molecular weight IgD (presumably IgD complexes) was measured with a radioimmunoassay using monoclonal anti-IgD antibody; results are expressed as the percentage of a positive control serum containing 739 ng IgD complexes/ml.

Patients were immunized with the secondary antigen tetanus toxoid and specific antibodies in the IgG and IgD class before and after immunization were measured by an enzyme-linked immunosorbent assay (ELISA) (15). Immunization with 1 mg of the primary antigen Helix pomatia haemocyanin (HPH) was performed subcutaneously in the deltoid region, and class-specific antibody levels (IgM, IgG, IgA, and IgD) were measured by an ELISA in serum obtained before and 14 and 42 days after immunization; HPH antibodies were expressed as a percentage of a positive reference sample as described (16).

In vitro proliferative responses of peripheral blood mononuclear cells to the mitogens phytohemagglutinin (PHA), pokeweed mitogen (PWM), and concanavalin A (Con A), to the antigens tetanus toxoid, Candida albicans, and HPH, and to allogeneic cells were determined with standard methods.

Circulating B cells were enumerated as surface Ig-positive cells and μ and δ expression was determined as described (17). T-cell numbers were determined using the monoclonal antibody OKT3 (CD3) (Ortho Pharmaceuticals, Raritan, NJ).

Bone marrow specimens were analyzed for plasma cells by cytoplasmic immunofluorescence for IgM, IgG, IgA, and IgD (18). Also, combined staining for the presence of surface IgM (slgM) and slgD on small cytoplasmic IgM (clgM)-positive cells, on large clgM-positive, and on large clgD-positive cells was performed.

RESULTS

Clinical findings and levels of serum IgM, IgG, IgA, IgD, and IgE are presented in Table II. All 17 patients had an elevated serum IgD (range, 175–5300 IU/ml). Patients 1 to 8 suffered from a syndrome characterized by periodic fever from the age