Long-Term Follow-Up of Anti-IgA Antibodies in Healthy IgA-Deficient Adults

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A follow-up study of anti-IgA antibodies in 159 healthy blood donors with severe deficiency of serum IgA (<0.05 mg/L) and in 45 donors with decreased serum IgA levels (0.05–799 mg/L), identified in 1971–1980, was carried out. Initially anti-IgA antibodies were determined by a hemagglutination (HA) method and two reexaminations were done in 1990–1992 by an enzyme immunoassay. The median follow-up period was 19 years, during which anti-IgA level was changed considerably in only four persons, increased in two, and high level antibodies (>1/1000 by HA) appeared in two. In reexaminations anti-IgA antibodies were found in 30 (19%) subjects with severe IgA deficiency and the antibody levels remained relatively constant in those who had high and medium antibody levels. Anti-IgA antibodies were not found in subjects with decreased, but detectable serum IgA. Thus it seems that only those healthy adults who have severe IgA deficiency develop anti-IgA antibodies and their anti-IgA levels remain fairly constant. Of the 159 subjects with severe IgA deficiency, 66 had a history of IgA exposure, but no correlation to anti-IgA development was noted.

KEY WORDS: Anti-IgA antibodies; IgA deficiency; immunodeficiency; IgA content; follow-up studies.

INTRODUCTION

Occurrence of antibodies against human immunoglobulin A (IgA) in patients with selective serum IgA deficiency was first described by Fudenberg et al. in 1968 (1). These antibodies belong to IgG class and can be either class specific with broad reactivity (1–4) or subclass- (5, 6) and allotype- (3, 7, 8) specific with narrow reactivity. Class-specific anti-IgA antibodies have been found in 10–42% of IgA-deficient blood donors (6, 9–12) and in 63% of IgA-deficient children (5). The stimulus leading to the production of these antibodies is unclear, and only some of the cases can be explained by a history of exposure to IgA (4, 9, 10, 13). Weak anti-IgA antibodies reacting only with one particular IgA protein used as antigen in the test, and which are not inhibited by normal human serum, have been found also in subjects with normal concentration of serum IgA (1–3, 6, 14).

Class- (2, 4, 12, 13, 15) or perhaps allotype- (3, 7, 8) specific anti-IgA antibodies of IgG class may cause an anaphylactic transfusion reaction following an injection or infusion of products containing IgA. The severity of the reaction has been related to the antibody titer and the amount of IgA infused (12, 15–19). Anti-IgA antibodies of IgD, IgE, and IgM class have also been described, but their clinical significance is unclear (15, 18, 19). Weak anti-IgA antibodies found in subjects with normal serum IgA have not been associated with severe transfusion reactions (2, 12, 14).

We have done a long-term follow-up study of anti-IgA antibodies in healthy subjects with severe deficiency of serum IgA (<0.05 mg/L) and with decreased (0.05–799 mg/L) concentration of serum IgA. The significance of IgA exposure to the existence of anti-IgA is also estimated.

MATERIAL AND METHODS

Subjects. Between 1971 and 1980, 204 healthy blood donors (60 female and 144 male) with primary selective deficiency of serum IgA were identified (20). The same subjects were studied again in 1990 and 1991–1992 for IgA deficiency using an enzyme immunoassay (21) and 159 of them were found to have severe IgA (<0.05 mg/L) deficiency and 45 decreased concentration (0.05–799 mg/L) of serum IgA (22). Their median age was 24 years (range 18–61) at the time of the initial screening and 41 years (range 29–79) at the first follow-up sampling in 1990. The first follow-up samples were collected between February and September 1990 and the second
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ones (from 194 subjects) between November 1991 and April 1992. The median follow-up period from the initial screening was 19 years (range 12–21), and the median interval between taking the two follow-up samples was 23 months (range 16–26). In 1990, 237 age- and sex-matched blood donors were studied as controls. Their serum IgA concentrations were verified to be normal by an immunoturbidimetric method (Kone Specific Automated Clinical Chemistry Analyzer, Kone Instruments, Espoo, Finland).

Methods. Between 1971 and 1989 anti-IgA antibodies were determined by a hemagglutination (HA) method using 10 isolated IgA myeloma proteins as antigens (4, 9). Different myeloma proteins gave slightly variable anti-IgA titers, and the highest observed titer for each sample was accepted as the initial anti-IgA level for this study. The lowest detectable titer was 1/16. Initial anti-IgA results were available for 185 of the 204 subjects (9; M. Heikkilä and J. Koistinen, unpublished observations).

In the follow-up study of 1990–1992 anti-IgA antibodies were determined by an enzyme immunoassay (EIA) (23). This method is based on the use of purified polyclonal human serum IgA as the coating antigen and an affinity purified alkaline phosphatase-conjugated rabbit anti-human IgG (IgG fraction; Dako A/S, Glostrup, Denmark) as the detecting antibody. A serum, which was designated to contain 12,000 arbitrary units of anti-IgA per liter (AU/L), was used as a standard. This value was based on the mean anti-IgA antibody titer obtained by EIA, and it correlated well with the HA titer for the same serum sample. This enabled the comparison of the earlier HA results with those obtained now by EIA. The lowest quantifiable concentration by the EIA method is 7 AU/L. The IgA specificity of a positive finding was confirmed by an inhibition test, in which pooled normal human serum inhibits the binding of specific antibodies by over 80%. Samples of those who had anti-IgA antibodies in both follow-up determinations of 1990–1992, were also tested by HA using a commercial IgA myeloma protein (Cappel Research Products, Organon Teknika, Turnhout, Belgium) and one of the 10 initially isolated IgA myeloma proteins (9) as antigens. The highest observed titer was accepted as the anti-IgA level.

Information on IgA Exposure. All subjects filled a questionnaire concerning prior blood transfusions, operations, immunoglobulin injections, and pregnancies. The given information was verified by a personal interview and from patient records. Prophylactic use of immunoglobulin could be verified only in a few cases. The amount of IgA in the blood products was estimated from the mean value of the reference range for serum IgA in adults.

RESULTS

Serum Anti-IgA Antibodies. Anti-IgA antibodies were found in at least one of the two follow-up examinations in 30 (19%) of the 159 subjects with severe IgA deficiency but in none of those with decreased or normal concentration of serum IgA (Table I). Nine of the 30 subjects had high (>1000 AU/L), five had medium (100–1000 AU/L), and 16 had low (7–100 AU/L) levels of anti-IgA (Fig. 1). In the two follow-up determinations of 1990 and 1991–1992 (one subject did not give the second sample) anti-IgA levels remained fairly constant in those with high and medium levels, but in eight of the 16 subjects with low antibody level there were reversals from positive to negative or vice versa. The remaining 129 subjects did not have anti-IgA antibodies in the follow-up determinations. Four of them did not give the second sample.

The initial anti-IgA results of 1971–1980 were available for 144 of the 159 subjects with severe IgA deficiency, and anti-IgA antibodies had been found in 17 of them. In the follow-up determinations, nine had retained their antibody level, two (subjects 18 and 19 in Fig. 2) showed considerable increase (over fourfold) of

Table I. Anti-IgA Antibodies in Subjects with IgA Deficiency, Decreased or Normal Concentration of Serum IgA at Follow-up Sampling in 1990–1992

<table>
<thead>
<tr>
<th></th>
<th>S-IgA (mg/L)</th>
<th>n</th>
<th>With anti-IgA</th>
<th>No anti-IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe IgA deficiency</td>
<td>&lt;0.05</td>
<td>159</td>
<td>30 (19%)</td>
<td>129</td>
</tr>
<tr>
<td>Decreased serum IgA</td>
<td>0.05–799</td>
<td>45</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>Normal serum IgA</td>
<td>800–4,000</td>
<td>237</td>
<td>0</td>
<td>237</td>
</tr>
</tbody>
</table>

n = total number of subjects.

Fig. 1. Findings of anti-IgA antibodies in the two follow-up samples of 1990 and 1991–1992 in subjects with severe serum IgA deficiency. The results are expressed as arbitrary units per liter (AU/L) by EIA. The detection limit of EIA (7 AU/L) and limits for low (<100 AU/L), medium (100–1000 AU/L) and high (>1000 AU/L) levels of anti-IgA are indicated by dotted lines.