Alpha-1-antitrypsin levels and clinical symptoms in forty-eight children with selective IgA deficiency

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Abstract. Previous studies in adult patients with selective IgA deficiency have pointed towards a possible connection between combined IgA and alpha-1-antitrypsin deficiency and the development of bronchiectasis. Thus, investigations were conducted of serum alpha-1-antitrypsin levels and clinical symptoms in 48 children with selective IgA deficiency. However, alpha-1-antitrypsin deficiency was not found in this group of patients. Furthermore, radiographic signs of recurrent pneumonia restricted to certain fields of the lungs, suggestive of bronchiectasis, were not observed in the patients. Thus, although a highly selected group of children with selective IgA deficiency was studied, a connection between IgA deficiency and alpha-1-antitrypsin deficiency was not obvious.

Key words: IgA deficiency – Alpha-1-antitrypsin levels

Introduction

Lung diseases may be associated with hypogammaglobulinemia, cystic fibrosis, alpha-1-antitrypsin (AAT) deficiency and allergy. Casterline et al. [3] and Østergaard [11] drew attention to a possible connection between IgA and AAT deficiency, especially in individuals with severe respiratory tract infections associated with emphysema and bronchiectasis.

The present paper presents the results of investigations of serum AAT levels, clinical symptoms and radiographic examination in 48 children with selective IgA deficiency. The significance of the findings is discussed.

Materials and methods

Forty-eight children, aged 3 to 14 years (median 8½ years) were studied, who were referred to our department with recurrent and chronic respiratory tract infections and/or various allergic diseases—mainly asthma—in whom no or very little IgA was detected in serum or saliva, but who had normal IgG levels. None had Giardia lamblia or cystic fibrosis, and none of them received phenytoin, penicillamine or other drugs known to cause secondary IgA deficiency [9]. Clinical symptoms such as recurrent respiratory tract infections with the culture of pathogenic bacteria from the throat (more than four incidences per year), the presence of allergic or autoimmune diseases, and evidence of bronchoctasis or emphysema on X-ray of their chests were recorded in all the patients.

Controls. Fifty-four healthy controls from the same geographical area as the patients were selected, matching the patients in age. The age range of the controls was 2–15 years (median 8½ years). None of the controls had experienced severe respiratory tract infections or atopic diseases, and none had first relatives with allergic diseases.

Serum IgG, IgA and IgM, and saliva IgA assays were performed by a sensitive electroimmuno technique. The method, which has been described in detail elsewhere [12] allowed the detection of IgA in serum of 0.01 g/l and in saliva of a concentration of 0.007 g/l. Serum IgE was measured with a paper-radio-immuno-sorbent-test (Pharmacia, Copenhagen). The sensitivity of detection of IgE in serum by this method was 5 UI/ml. Specific serum IgE to pollen, animal danders, moulds and house dust mites were determined by a radio-allergo-sorbent-test (RAST, Pharmacia, Copenhagen), and a RAST-class more than 2 was considered positive.

Assay for AAT levels in serum was performed by an immunochemical method, which also has been described in detail elsewhere [1].

Statistical analysis of the results was done by the Mann-Whitney U-test.

Results

Serum and saliva Ig levels and serum AAT levels of the patients and the controls are listed in Table 1. In 32 IgA deficient patients, IgA was not present either in serum or in saliva. In the remaining 16 patients, IgA was present in serum in concentrations from 0.015 to 0.21 g/l (median 0.09 g/l), and in saliva in concentrations from 0.011 to 0.019 g/l (median 0.014 g/l). The level of IgG in serum was within the same range as that of the controls, whereas a significant increase in serum IgM as well as in serum IgE was observed in the patients as compared to the serum IgM and IgE levels of the controls. However, no significant difference between the serum AAT levels in the patients and the controls was found. The clinical symptoms of the IgA deficient patients appear in Table 2. Bronchial asthma alone or associated with atopic dermatitis or rhinitis was common (19 patients). Furthermore, recurrent sinopulmonary infections, often with the culture of pneumococci and/or Hemophilus influenzae but without evidence of allergic disorders were next in frequency (17 patients). Autoimmune diseases were not pre-
Table 1. Ig- and AAT-levels in the IgA deficient patients and their age-related controls

<table>
<thead>
<tr>
<th></th>
<th>Serum immunoglobulin levels</th>
<th>Saliva IgA (g/l)</th>
<th>Serum AAT (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG (g/l)</td>
<td>IgA (g/l)</td>
<td>IgM (g/l)</td>
</tr>
<tr>
<td>The IgA deficient children (48)</td>
<td>Range</td>
<td>7.8–15.8</td>
<td>&lt; 0.01–0.21</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>10.6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Healthy age-related controls (54)</td>
<td>Range</td>
<td>6.4–14.6</td>
<td>0.48–2.6</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>10.1</td>
<td>1.10</td>
</tr>
</tbody>
</table>

Table 2. Clinical symptoms in the IgA deficient children

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Recurrent respiratory infections without allergy</th>
<th>Asthma</th>
<th>Asthma and rhinitis</th>
<th>Asthma and atopic dermatitis</th>
<th>Asthma, atopic dermatitis and rhinitis</th>
<th>Glomerulonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forty-eight IgA deficient children</td>
<td>17</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

sent in any of the patients apart from two patients with relapsing glomerulonephritis, which responded well to steroids.

Of the 19 patients with allergic diseases, all had positive RAST to one or more allergens, in 14 and 12 patients, respectively RAST was positive to animal danders or house dust mites, 6 had positive RAST to moulds, whereas only 3 patients had positive RAST to pollen. Only some of the IgA deficient children without recurrent infections or allergic disorders had a raised serum IgE or positive RAST. Among the IgA deficient children without recurrent infections or allergic disorders, short, recurrent febrile episodes without an obvious “focus of infection” were very common.

Radiographic examinations of the lungs in the patients showed a varying degree of emphysema, but no signs of bronchiectasis.

Discussion

AAT deficiency is an autosomal, recessive hereditary disease, and both the homozygous and the heterozygous states have been implicated in the occurrence of early adult bronchitis and emphysema, and in some cases with the development of bronchiectasis [4, 5, 7, 11], but the aetiology remains unclear. Furthermore, some children with IgA deficiency are prone to develop recurrent respiratory tract infections [2,8], and, in addition, IgA deficiency is frequently found in children with bronchial asthma [10]. On the other hand, chronic lung disease with or without bronchiectasis is not common among children with isolated IgA deficiency [9].

Tarkoff et al. [13] suggested that children with asthma or asthmatic bronchitis may represent a *forme fruste* of the AAT phenomenon. However, Katz et al. [6], who studied AAT levels and AAT phenotypes in 151 children with asthma compared to normal children, found that both groups revealed similar incidences of AAT deficiency. On the other hand, these authors found the Z variants in a greater percentage of steroid-dependent patients with asthma. In addition, we studied AAT levels in a total of 411 children with asthma and found none with AAT deficiency [10].

Casterline et al. [3] studied the inter-relationship of IgA and AAT. In 23 AAT deficient adult patients, IgA levels were normal. However, in fifteen adult patients with isolated IgA deficiency, three had AAT deficiency, one had the phenotype PiZZ, and another two the heterozygous state of PiMS and PiMZ. All three of them had considerable respiratory tract infections, two of them with bronchiectasis. The authors did not mention, if the latter had the Z variants. Recently, we studied a five-year-old boy with asthma and serious attacks of pulmonary infections [11]. This child also had a selective IgA deficiency and deficiency of AAT with the phenotype PiMZ. Repeated X-ray examinations of his chest gave suspicions of bronchiectasis of his mid-lobe. The parents of this patient, however, refused to have a bronchographia made, and in the latter patient as well as in the present patients with IgA deficiency, only the performance of a bronchographia can confirm or exclude the presence of bronchiectasis.

The present patients, who included a considerable number of children with IgA deficiency associated with recurrent respiratory tract infections and/or bronchial asthma, revealed none with AAT deficiency. Thus, a connection between selective IgA deficiency and AAT deficiency is not obvious. However, since the frequency of AAT deficiency is 1:3000 in a normal population [4], our data do not exclude the possibility that the frequency of AAT deficiency in IgA deficient patients might be higher than in the control population.

Among the present patients, very elevated serum IgE and IgM levels were a common finding, which might be due to this group of children being selected with a history of recurring respiratory tract infection and/or allergic diseases. However, it is well known that unselected individuals with IgA deficiency are often asymptomatic [9].

Normally, heterozygous AAT individuals have an intermediate deficiency of AAT and are more protected from emphysema and bronchitis than those with homozygous deficiency. As indicated by a few reported cases with combined