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Special Article

The Heterogeneity of IgA Deficiency

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INTRODUCTION

IgA deficiency (IgAd) was initially described not only in two healthy individuals (1) but also in patients with various diseases (2, 3). Some had an increased frequency of infections, while others had autoimmune diseases, atopy, malabsorption, tumours, or various less common problems.

The autoimmune diseases, as well as tumours, atopy, and malabsorption, may well be causally related to the IgAd but the involved mechanisms are unknown. The increased frequency of infections seen in many patients may be related more directly to the antibody deficiency. The lack of serum IgA is accompanied by a deficiency of secretory IgA, which is a major component in the defense of mucosal membranes (4). Actually more than half of the body's total content of all antibodies consists of IgA. Against this background it is surprising that not many more individuals with selective IgAd have an increased tendency to infections.

This article discusses the concept that IgAd is a heterogeneous group of conditions ranging from well-compensated healthy individuals to those with an uncompensated deficiency who can have relatively severe infectious problems. The latter group should receive more clinical attention than is usually given today.

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IgA DEFICIENCY AND INFECTIONS

The natural history of disease in patients with frequent infections and IgAd shows that they usually initially have repeated upper respiratory tract infections. This was seen in about 60% of a group of IgAd patients (5). Lower respiratory tract infections followed later in only 3 of 18. In contrast, such infections appeared in most patients with common variable immunodeficiency (CVID) within a few years after the onset of their disease, which was characterized by recurrent upper respiratory infections, otitis, and sinusitis. The substantial risk of developing lung damage often reported in CVID patients (6) is not a major threat to IgAd individuals. However, lung function is significantly impaired among those IgAd patients who are also deficient in IgG subclasses (7, 8). We have noted also a few patients with IgAd without IgG subclass deficiency who had signs of lung damage as well and significantly decreased mucociliary function, presumably secondary to the recurrent upper respiratory infections. Infections in sites other than the respiratory tract are much less frequent.

COMPENSATORY MECHANISMS IN IgA DEFICIENCY

Brandtzaeg *et al.* originally described the increase in the number of IgM-producing cells in the mucosa of IgAd individuals (9). Mellander *et al.* (10) found that IgM antibodies against *Escherichia coli* and poliovirus antigens were significantly elevated compared to normals in nasal secretions in IgAd individuals without any increased susceptibility to

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infections. However, those with IgAd and frequent infections did not show a similar elevation of the IgM antibody concentration, possibly providing one explanation why they had these infections. Furthermore, Brandtzaeg *et al.* (11) found that an increased number of IgD-producing immunocytes in the nasal mucosa was not associated with a clearly decreased number of infections. Those IgAd individuals who, in contrast, had many IgM immunocytes had no increased infectious problems (11). The protective efficiency of increased mucosal production of IgM is presumably related to the fact that IgM can be transported onto the mucosa via secretory component in the absence of IgA. This does not happen for IgD (11).

We have also noted a striking increase in the number of goblet cells in the nasal mucosa of many IgAd patients (12, 13). More than 50% of the epithelium consisted of goblet cells in some individuals (13). The increase in goblet cells seemed to require normal T-cell function, and no or few goblet cells were seen when T-cell deficiencies were present, as, for example, in CVID patients. It has not yet been determined whether the increase in goblet-cell numbers is secondary to the patient's condition or may be a compensatory mechanism helping to protect the IgAd mucosa.

Vaccination of selectively IgAd individuals with frequent infections using a meningococcal capsular polysaccharide vaccine showed a very high response in 5 of 17 as determined with a radioimmunotechnique. Three showed a normal response to the capsular polysaccharide C, but a deficient response was noted in nine (14). Vaccination may thus be used to discern abnormalities outside the IgA isotypes in the IgAd patients. One consequence of the abnormal reactivity to a vaccine in selective IgAd was recently illustrated by the prolonged excretion of poliovirus after peroral vaccination with the live vaccine in IgAd individuals (15). Aberrations were also seen in an analysis of the IgG antibody response to pneumococcus types 1 and 14 in IgAd patients vaccinated with a 14-valent pneumococcus vaccine. Responses of controls and IgAd patients to type 1 polysaccharide were generally poor, although the IgAd patients had significantly higher pre- and postvaccination levels of IgG1 and IgG3 antibodies against the type 1 polysaccharide than controls. Type 14 polysaccharide induced good responses in all four IgG subclasses, with significantly greater postimmunization IgG3 antibody concentrations in the IgAd group than in controls. It seems that dysregulation of vaccine responses in IgAd can result in sub- as well as supernormal antibody levels and that these regulatory abnormalities can include the IgG subclasses whether or not their total levels are decreased. This is of special interest since we noticed a few years ago that IgA deficiency may be associated with IgG subclass deficiency (16). Those patients with the combined deficiency seemed to have more serious problems with infections than those with isolated IgAd, showing significantly more often not only impaired lung function, but also in some instances bronchiectasis as well as asthma (7, 8). The heterogeneity of IgAd was also illustrated by low levels of interferon α in some (17, 18). In contrast patients with common variable hypogammaglobulinemia produced significantly more interferon γ as well as α than controls (18). As a possible consequence we found increased NK-cell activity in these patients, whereas the IgAd patients were not grossly abnormal in this cell function (19).

It was notable that HLA typing of IgAd individuals showed that in the healthy group there was a strong association with HLA B8 and DR3. In contrast, IgAd patients with frequent infections showed no association with these antigens, but a significant association with HLA B40 was demonstrated (20).

TREATMENT OF IgA DEFICIENCY

IgAd patients have usually not been given immunoglobulin prophylaxis even when they have had considerable problems with recurrent infections, first, because it has been considered that the immunoglobulins would not compensate efficiently for the defect in the host defense at the mucosal level and, second, because of the risk of inducing antibodies to IgA, potentially causing severe side effects on injection of IgA-containing material. As to the first argument, it should be noted that adequate prophylaxis with immunoglobulin preparations consisting almost exclusively of IgG is successful in preventing infections in patients lacking IgG and IgM, as well as IgA. This could be taken as evidence that IgG can compensate also for the lack of mucosal IgA.

The argument concerning the possible side effects of Ig prophylaxis caused by anti-IgA is no longer definitely valid if immunoglobulin preparations are used which are depleted of IgA. Using such a preparation it was possible to give an immunoglobulin preparation repeatedly to six immunodeficient

patients with demonstrable anti-IgA antibodies without any untoward effects and without any increases in their titers of anti-IgA (22). In the seventh patient, however, there was, after several uneventful infusions, a dramatic reaction, obviously due to the very small amounts of IgA remaining in the preparation. Analyzing his anti-IgA a continuous increase in anti-IgA titers could be registered during the period in which the series of infusions had been given. This patient had reacted strongly to previous prophylaxis with other materials and the present reaction could presumably have been avoided if his anti-IgA antibody titers had been followed continuously. He later tolerated another Ig preparation very low in IgA.

We found anti-IgA to be more common in various antibody deficiency syndromes such as IgAd, IgAd + IgG subclass deficiency, and hypogammaglobulinemia than previous researchers, when using not only indirect hemagglutination but also enzyme-linked immunosorbent assay (ELISA). It may be that the tendency to produce increased levels of anti-IgA is linked to the form of antibody deficiency. The highest frequency of anti-IgA appeared in those with combined IgA-IgG subclass deficiency (21). High titers of anti-IgA also were reported in IgAd individuals with low IgG4 and IgE (22). The question whether or not Ig prophylaxis can help patients with selective IgAd and frequent infections cannot be answered presently and controlled studies are needed. Those who have combined IgA–IgG subclass deficiency most probably should be given Ig prophylaxis because of their increased risk of attracting lung damage. Preliminary observations suggest that such prophylaxis can be helpful (23).

Further studies of IgAd should provide a better understanding of how the deficiency can be compensated for by various mechanisms and also define the various combined dysregulations and deficiencies better. Thus the patient's condition and need for more active measures of treatment and prophylaxis may be evaluated more efficiently.

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