

## **Annotations**

# Clinical significance of IgA deficiency

IgA is one of the five classes of immunoglobulin found in biological fluids. It is the major secretory immunoglobulin and is widely distributed in all mucosal secretions as a dimeric molecule linked by a joining chain and a third molecule, the secretory piece. The dimeric form is resistant to proteolytic digestion and IgA antibodies are important in the protection of mucous membranes against invasion by pathogens.<sup>1</sup> The function of serum IgA antibodies, which mainly exist in monomeric form, is unclear. Low serum IgA, however, is a useful marker of secretory IgA deficiency which almost invariably accompanies it. There is only one reported case of absent secretory IgA in the presence of normal serum IgA and this was associated with an absence of the secretory piece.<sup>2</sup> There are two serologically and structurally distinct IgA subclasses, IgA<sub>1</sub> comprises 90% of circulating IgA, but the IgA found in secretions is equally distributed between IgA<sub>1</sub> and IgA<sub>2</sub>.<sup>3</sup>

IgA deficiency with normal concentrations of other immunoglobulin classes (isolated IgA deficiency) was the first<sup>4</sup> and is the most common immunoglobulin deficiency described. The genetic basis of IgA deficiency is not known but there are associations with certain HLA-types, healthy IgA deficient individuals having an excess of HLA-B8 and DR3 and symptomatic ones an increased frequency of HLA-B40.<sup>5</sup> IgA deficiency usually occurs sporadically but is found with variable inheritance patterns within some families. The section of DNA coding for the  $\alpha$  heavy chain of IgA within the immunoglobulin gene has always been found to be present in isolated IgA deficiency. However no  $\alpha$  chain messenger RNA was generated in polyclonally activated B-lymphocytes from IgA deficient individuals, making a DNA to RNA transcriptional defect possible in such patients.<sup>6</sup>

The incidence of IgA deficiency is approximately one in 500 of the general population.<sup>1</sup> Most of these individuals are healthy but a minority have significant symptoms. In these patients frequent upper and lower respiratory tract infections and middle ear infections predominate and in some significant organ damage such as bronchiectasis may result.<sup>7</sup> In subjects with allergic disorders and autoimmune diseases the incidence of IgA deficiency is higher, sometimes approaching one in 100.<sup>1</sup> Weak associa-

tions with IgA deficiency occur in coeliac disease, systemic lupus erythematosus and other autoimmune disorders,<sup>1</sup> gastrointestinal disease,<sup>8</sup> and some malignancies.<sup>9</sup> The dichotomy between symptomatic and asymptomatic IgA deficient individuals remains, however, often making the significance of the finding in individual patients unclear. A further complication is the transience of IgA deficiency, both in adults<sup>10</sup> and particularly in children,<sup>11</sup> where it may represent delayed maturation of the humoral immune system. During ontogeny IgA is the latest of the immunoglobulin classes to develop, and normal serum and mucosal concentrations do not reach adult concentrations until puberty. Reversible IgA deficiency is also induced by some drugs including phenytoin.<sup>12</sup>

There are a number of possible explanations for the presence of symptoms in only a minority of individuals with isolated IgA deficiency.<sup>13</sup> The severity of the deficiency may be important as children with very low concentrations of IgA (<0.05 g/l) had a higher incidence of pneumonia than those who were also IgA deficient but had concentrations >0.05 g/l but < -2 SD below the mean for age. Furthermore, 50% of this latter group had only transient deficiencies but the more severe deficiencies were permanent.<sup>10</sup> Most even profoundly IgA deficient individuals are still asymptomatic, however, and in these subjects mechanisms which compensate for the lack of IgA are probably operating. One such mechanism may be the increased local production and passage of IgM into nasal secretions and saliva seen in asymptomatic but not symptomatic individuals.<sup>14</sup> A third reason for the discrepancy of symptoms between individuals with isolated IgA deficiency may lie in variable associations with other covert immunodeficiencies. For example, low concentrations of certain subclasses of IgG, particularly IgG<sub>2</sub> and IgG<sub>4</sub>, are found in approximately 15% of patients with IgA deficiency,<sup>15</sup> though in one study of 60 IgA deficient children this combination did not correlate with an increased incidence of infection.<sup>16</sup> Furthermore, qualitative<sup>17</sup> or quantitative<sup>18</sup> abnormalities in the IgG antibody response to infection or immunisation have been described even in the presence of normal or high total IgG and IgG subclass concentrations. Pulmonary damage is more common in IgA deficient

adults who have associated immunodeficiencies,<sup>19</sup> though it may also occur in IgA deficient individuals without demonstrable IgG abnormalities.

How then should the paediatrician, or more importantly the general practitioner, approach the child with isolated IgA deficiency? Asymptomatic individuals or those with very minimal symptoms should be regarded as having a compensated immunodeficiency. Early recourse to antibiotics during intercurrent infections is justified, and vigilance should be maintained for evidence of organ damage, poor growth, or allergic symptoms. Their detection is an indication for careful assessment of middle ear and pulmonary status. In these subjects more detailed immunological investigations may be undertaken, but the initial approach is based on the clinical situation.

Associated allergic and other symptoms (autoimmunity, cough, sputum production, conjunctivitis, etc) should be controlled, and chest physiotherapy instituted, and middle ear drainage considered, especially if organ damage is evident. After this, a sequence of treatment should be followed until a satisfactory clinical response is obtained. The sequence consists of: (a) vigorous early antibiotic treatment during all infections; (b) prophylactic antibiotic treatment (once daily cotrimoxazole is useful in this context); and (c) intravenous immunoglobulin infusions.

Requirement for the second stage in this sequence should be preceded by further immunological investigation and before recourse to the third, assessment by a paediatric immunologist is desirable. Intravenous immunoglobulin should only be given if infections are severe or frequent enough to cause significant disability. They should be used with caution, as IgA deficient individuals occasionally have severe reactions to immunoglobulin infusions caused by the development of antibodies to IgA.<sup>20</sup> Immunoglobulin preparations low in IgA may be preferable and monitoring for IgA antibodies is recommended.<sup>20</sup> Liver function tests should be measured regularly as non-A non-B hepatitis has, on rare occasions, been transmitted by some intravenous immunoglobulin preparations.<sup>21 22</sup>

There are no accurate data on prognosis for symptomatic children, but there is a tendency to improve with age and probably at least 50% will not be symptomatic as older children or adults. The IgA concentration may become normal in those with less severe deficiencies any time between six months after the first assessment up to the age of 14 years,<sup>11</sup> and on occasions thereafter.<sup>10</sup> Symptoms may improve despite persistence of the deficiency, presumably as the maturing immune system develops compensatory mechanisms. On rare

occasions the converse may be true and IgA deficiency may precede the development of a more generalised hypogammaglobulinaemia. The discovery of IgA deficiency should alert the physician that he or she may be dealing with a patient with compromised immunity to infection. Patients should be monitored closely with a view to preventing the long term sequelae of IgA deficiency.

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