Screening of blood donors for IgA deficiency: a study of the donor population of south-west England

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SUMMARY

Altogether 29 745 English blood donors were screened for IgA deficiency by double diffusion analysis; 57 had apparent absence of IgA, a frequency of 1:522. Further examination by the more sensitive haemagglutination inhibition assay revealed 34 samples having no detectable IgA, a frequency of 1:875. All donors negative by double diffusion analysis were tested for the presence of antibodies to IgA. Six class specific anti IgA antibodies and four anti IgA antibodies of limited specificity were detected. Three of these had the specificity anti α2 and one anti A2m(2). The 34 IgA deficient donors detected provide a source of IgA deficient blood for transfusion to patients with anti IgA antibodies.

Selective IgA deficiency is the most common immunoglobulin deficiency. It has been shown to be associated with numerous disorders including ataxia telangiectasia, recurrent respiratory tract infection, coeliac disease, and many autoimmune diseases (Hobbs, 1968; Ammann and Hong, 1971; Bergström et al., 1973). Selective IgA deficiency has also been found in apparently healthy blood donors with a frequency ranging from 1:300 to 1:3000 (Johansson et al., 1968; Natvig et al., 1971; Frommel et al., 1973; Koistinen, 1975; Vyas et al., 1975).

The relatively high frequency of this major immunoglobulin deficiency in turn gives rise to problems in transfusion practice. Individuals with IgA deficiency may have antibodies to IgA (Vyas and Fudenberg, 1971). These antibodies, usually known as ‘class specific’ anti IgA antibodies because they react with all IgA proteins tested, can be the cause of serious anaphylacthic transfusion reactions (Vyas et al., 1968b; Schmidt et al., 1969; Bjerrum and Jersild, 1971; Leikola et al., 1973; Pineda and Taswell, 1975). In addition, some patients with apparently normal levels of IgA can produce antibodies of limited specificity, reacting with some but not all IgA proteins. These antibodies may also cause transfusion reactions (Vyas et al., 1968b; Pineda and Taswell, 1975).

In cases of transfusion reaction due to anti IgA antibodies it is important to provide compatible blood or plasma derived from IgA deficient donors. The aim of this study was to establish a panel of IgA deficient blood donors to meet this need.

Material and methods

SCREENING FOR IgA DEFICIENCY

Serum samples from 29 745 volunteer blood donors were tested by double diffusion analysis in a medium containing 1% agarose (BDH, Poole, UK), in phosphate buffered saline (PBS) pH 7.3 (Dulbecco ‘A’, Oxoid, Basingstoke, UK) using a monospecific anti-IgA serum. The anti-IgA serum was prepared by immunising rabbits with a pool of four purified monoclonal IgA proteins. The antiserum was rendered specific for IgA by absorption with a pool of purified monoclonal IgG and IgM proteins. The lowest level of IgA detected in this double diffusion system was defined as 40 μg IgA/ml serum using a standard serum (Hoechst Pharmaceuticals, Hounslow, UK). Those sera failing to give a line of precipitation in the double diffusion screening test were further examined in a haemagglutination inhibition system using five haemagglutinating doses of a human class specific anti-IgA serum (JM) and human group O red cells coated with IgAI protein (Vyas and Fudenberg, 1971). The lowest level of IgA detected in the haemagglutination inhibition system was 0.5 μg IgA/ml. Only sera which failed to show any inhibition of the agglutinator were classified as IgA deficient (that is, less than 0.5 μg IgA/ml).

DETECTION OF ANTIBODIES TO IgA, IgM, AND IgG

Antibodies to IgA were detected by passive haemagglutination assay using a panel of six IgA myeloma proteins (Table 1) by the chromic chloride method of Gold and Fudenberg (1967). Optimal conditions for
the coupling of the proteins were determined by the chequerboard method. The IgA coated cells were used at a concentration of 1% in PBS containing 2.5 mg/100 ml poly-vinylpyrolidone (PBS-PVP buffer) in V-shaped microtitre plates by the method of Vyas et al. (1968a). Sera were screened for antibodies at initial dilutions of 1/4 and 1/8 in PBS-PVP buffer. Antibodies detected in the screening tests were titrated and confirmed by specific inhibition tests using purified paraproteins as described by Vyas and Fudenberg (1971). Antibodies to IgM were detected by similar methods using a panel of four purified IgM paraproteins. Antibodies to IgG (Gm antibodies) were detected by incubating test serum at a dilution of 1/4 in saline with 2% saline suspensions of group O CDE/DE cells coated with incomplete anti-D (selected for their ability to coat certain Gm and Km antigens) for two hours at 20°C (Table 1).

### Table 1 Protein coats in passive haemagglutination tests

<table>
<thead>
<tr>
<th>Proteins</th>
<th>Immunoglobulin class</th>
<th>'H' chain allotype</th>
<th>'L' chain type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanks</td>
<td>IgA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watts</td>
<td>IgA</td>
<td></td>
<td>Lambda</td>
</tr>
<tr>
<td>Yeates</td>
<td>IgA</td>
<td></td>
<td>Kappa</td>
</tr>
<tr>
<td>Herbert</td>
<td>IgA</td>
<td></td>
<td>Kappa</td>
</tr>
<tr>
<td>Bruton</td>
<td>IgA</td>
<td>A2m (1)</td>
<td>Kappa</td>
</tr>
<tr>
<td>Schnell</td>
<td>IgA</td>
<td>A2m (2)</td>
<td>Lambda</td>
</tr>
<tr>
<td>Bennett</td>
<td>IgM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Box</td>
<td>IgM</td>
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<td>Kappa</td>
</tr>
<tr>
<td>Crumpler</td>
<td>IgM</td>
<td></td>
<td>Kappa</td>
</tr>
<tr>
<td>Turl</td>
<td>IgM</td>
<td></td>
<td>Lambda</td>
</tr>
<tr>
<td>Anti-D GD-78</td>
<td>IgG</td>
<td>Gm (1, 2, 17)</td>
<td></td>
</tr>
<tr>
<td>Anti-D GD-59</td>
<td>IgG</td>
<td>Gm (1, 2)</td>
<td></td>
</tr>
<tr>
<td>Anti-D GD-97</td>
<td>IgG</td>
<td>Gm (1, 17)</td>
<td></td>
</tr>
<tr>
<td>Anti-D GD-99</td>
<td>IgG</td>
<td>Gm (3)</td>
<td></td>
</tr>
<tr>
<td>Anti-D GD-110</td>
<td>IgG</td>
<td>G3m (5, 10, 11, 13, 14)</td>
<td></td>
</tr>
<tr>
<td>Anti-D GD-68</td>
<td>IgG</td>
<td>G3m (5, 10, 11, 14)</td>
<td></td>
</tr>
<tr>
<td>Anti-D GD-93</td>
<td>IgG Kappa</td>
<td>Km (1, 2)</td>
<td>Kappa</td>
</tr>
</tbody>
</table>

1IgA proteins purified by method of Fine and Steinbuch (1970); IgM proteins purified by method of Johnson (1970).
2Gm and Km coating sera supplied by Miss D. M. Brazier, Blood Group Reference Laboratory, Gatfifie Road, London, UK.

The 34 IgA deficient sera (<0.5 μg IgA/ml) and those sera with very low level IgA (0.5-40 μg IgA/ml) were examined for the presence of antibodies to IgA, IgM, and IgG by the passive haemagglutination method (see Methods) and the results are presented in Table 3. Antibodies specific for IgA but reacting with all six IgA coats (class specific) were found in six serum samples. Three samples contained antibodies specific for the IgA2 subclass of IgA (anti α2 antibodies) and one serum contained an antibody specific for the allotype A2m(2). Four samples contained anti IgM of limited specificity reacting with some but not all IgM coats. One sample contained an anti-Gm antibody specific for the Glm(1) allotype. In no case were anti IgA antibodies found in the 23 sera having very low levels of IgA (0.5-40 μg/ml).

### Discussion

The frequency of IgA deficiency has been the subject of study by a number of workers (Bachmann, 1968; Frommel et al., 1973; Hobbs, 1968; Johansson et al., 1968; Natvig et al., 1971; Koistinen, 1975; Vyas et al., 1975) and reported values vary from 1:300 to 1:3000. This variation, although reflecting differences
in the populations studied, is to some extent due to the different techniques employed to define IgA deficiency (immunodiffusion, passive haemagglutination, radioimmunoassay). The results presented here for blood donors in England (frequency 1:875 using passive haemagglutination inhibition) are in broad agreement with data obtained by other workers using the same methods; in America, Vyas et al. (1975) found a frequency of 1:886 from a series of 73,569 blood donors, and in Finland Koistinen (1975) found 1:507 from 64,588 donors. The more sensitive method of radioimmunoassay has not been employed in this study, but from the data of Koistinen (1975) it would be expected that some of the donors defined as IgA deficient in this report would be found to have very low levels of IgA by this method.

The presence of specific anti IgA antibodies in the serum of IgA deficient blood donors is well known. In this study six of 34 (18%) IgA deficient donors were found to have class specific anti IgA antibodies, a finding in broad agreement with that of other workers (Koistinen and Sarna, 1975; Vyas et al., 1975). In disease states associated with IgA deficiency the frequency of such antibodies is much higher, that is, 40-44% (Cassidy et al., 1969; Vyas et al., 1969; Ammann and Hong, 1971; Nadorp et al., 1973), and this may be related to the higher incidence of blood transfusion in such patients.

An interesting finding of this study has been the presence of anti IgA antibodies of limited specificity in four of the 34 IgA deficient donors. The presence of antibodies of limited specificity in IgA deficient individuals has not been widely reported (van Loghem et al., 1973; Nadorp et al., 1973).

Human antibodies to IgM are known to occur in normal donor populations (Leikola et al., 1971; Wells et al., 1973); as yet no clinical problems have been related to their presence and their significance remains unclear. The antibodies found in this study are of low titre (1/4-1/16) and so are unlikely to cause problems in transfusion.

The 34 IgA deficient donors detected form the basis of a panel of IgA deficient donors providing blood for transfusion to patients with anti IgA antibodies. Similar donor panels are also available in America, Canada, Denmark, and Finland (Vyas and Perkins, 1976).

We are indebted to Dr E. van Loghem, Amsterdam, for subtyping our IgA proteins and for confirming the specificity of antibodies detected; to Drs Koistinen and Leikola, Helsinki, for the gift of human anti IgA serum (JM) and IgA proteins; and to Dr Skvaril, Zurich, for the gift of plasma (Schnell) containing the IgA2 (A2m2) protein. We also thank Dr J. Bothamley, RTC Bristol for making available large quantities of plasma from patients with monoclonal proteins undergoing plasmapheresis. The technical help of many colleagues from RTC Bristol is gratefully acknowledged.

References


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