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# An investigation into the effect of the IgG antibody system on the susceptibility of IgA-deficient patients to respiratory tract infections

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## SUMMARY

Serum IgG subclass concentrations and IgG-tetanus toxoid antibody (IgG-TTab) responses were measured in IgA-deficient patients with severe respiratory tract infections ($n=11$), mild respiratory tract infections ($n=5$) or no increased susceptibility to respiratory tract infections ($n=15$). The severe infection group had lower IgG2 concentrations than the patients without infections ($P<0{\cdot}02$) and was the only group with IgG2-deficient patients (36%). The number of sera in which IgG4 was not detected was higher in patients with severe infections than in both normal controls (45% vs 10%, $P<0{\cdot}01$) and the other IgA-deficient patients (45% vs 20%), in part explained by a strong association with IgG2 deficiency. Subnormal IgG-TTab responses were demonstrated in 45% of patients with severe infections but in only one patient from each of the other two groups. Five patients with IgG2 deficiency and/or subnormal IgG-TTab responses were treated with gammaglobulin and apparently improved. There was a high serum concentration of IgG1 in 35% and IgG3 in 19% of the 31 patients, predominantly in those without severe infections. Thus a proportion of IgA-deficient patients have additional defects of IgG; IgG1 and IgG3 antibody responses may compensate for the IgA deficiency in asymptomatic patients.

**Keywords** IgA deficiency IgG subclasses gammaglobulin therapy

## INTRODUCTION

It has been conventional to consider that individuals with primary selective IgA deficiency have a uniform immune defect (Ammann & Fudenberg, 1982), but it is now apparent that heterogeneous immune defects in addition to serum IgA deficiency and deficient secretory-IgA (s-IgA) antibody responses are sometimes present. These include IgE deficiency (Polmar *et al.*, 1972), defects of T-lymphocyte function *in vitro* (De la Concha *et al.*, 1980), impaired neutrophil chemotaxis (D'Amelio *et al.*, 1980; Melamed *et al.*, 1985), IgG subclass deficiency (Oxelius *et al.*, 1981; Ugazio *et al.*, 1983) and subnormal primary or secondary systemic antibody responses (De Graeff *et al.*, 1983; French & Harrison, 1984a; Umetsu *et al.*, 1985). It is, therefore, possible that the variable susceptibility of IgA-deficient patients to respiratory tract infections (Asherson & Webster, 1980) is not only related to the protective effects of compensatory secretory-IgM (s-IgM) and systemic -IgG antibody responses in some IgA-deficient individuals (Plebani *et al.*, 1983; Ogra *et al.*, 1974), but also to the presence or absence of additional immune defects. There is, indeed, evidence that those

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IgA-deficient patients with additional IgG subclass deficiency are most susceptible to respiratory tract infections (Oxelius *et al.*, 1981; Ugazio *et al.*, 1983).

There might, therefore, be a subgroup of IgA-deficient patients with additional defects of IgG antibody responses who might benefit from gammaglobulin therapy (Van der Giessen, Reerink-Brongers & Algra-van Veen, 1976; Koistinen, Heikkilä & Leikola, 1978; Bjorkander *et al.*, 1985), providing that the problems associated with giving gammaglobulin therapy to IgA-deficient patients (Buckley, 1985) can be surmounted. Hence, we have studied the relationship between additional defects of IgG antibody responses and respiratory tract infections in IgA deficient patients, not only by assaying serum IgG subclasses but also by measuring IgG-tetanus toxoid antibody responses. The effect of gammaglobulin therapy was then assessed in those patients with additional defects.

## PATIENTS AND METHODS

*Patients.* Thirty-one patients with selective IgA deficiency were recruited to the study in two ways. A proportion were referred to an immunology clinic from general medical and chest clinics because of an increased susceptibility to respiratory tract infections; IgA deficiency had been demonstrated in most before referral but serum IgG subclass concentrations were not measured until entry into the study. The remaining patients were identified from serum samples passing through the immunology laboratory during the course of investigations for various diseases. All patients gave their consent to take part in the study. A standard clinical questionnaire was completed with particular emphasis being given to infection history. Based on the infection history, three groups of patients were defined.

(a) Six male and five female patients of mean age 36 (range 9–59) who had presented with severe respiratory tract infections. These infections were characterized by purulent bronchitis, and pneumonia in a minority of patients, which required treatment with frequent courses of antibiotics and resulted in significant loss of time from work or school.

(b) Three male and two female patients of mean age 32 (range 20–39) with mild respiratory tract infections characterized by recurrent and/or persistent upper respiratory tract infections only.

(c) Eight male and seven female patients of mean age 36·5 (range 16–60) with no abnormal susceptibility to respiratory tract infections but various other diseases.

*Serum IgG subclasses.* Serum IgG subclass concentrations were measured in serum samples which had been taken before any immunizations were performed and had been stored at −20°C. The assay method and values for healthy adults are described elsewhere (French & Harrison, 1984b). The assay was calibrated with either of two standard sera: WHO 67/97 or SPS-01 (Supra Regional Protein Reference Unit, Sheffield) which has been calibrated against WHO 67/97 (Milford Ward *et al.*, 1984).

*IgG-tetanus toxoid antibody (IgG-TTab) responses.* Serum concentrations of IgG-TTab were measured 2 weeks after a 'booster' immunization with tetanus toxoid as described previously (French & Harrison, 1984a). Immunization studies were performed between episodes of infection and at a time when patients were not taking drug therapy which could have influenced antibody responses.

*Anti-IgA antibodies.* Sera were tested for anti-IgA antibodies at presentation; in five patients, sera were also tested after at least 2 years of gammaglobulin therapy (see below). Titres of anti-IgA antibodies were measured by an enzyme-linked immunosorbent assay (ELISA) as follows. Human IgA (Sigma, Poole, UK) diluted to 100 μg/ml in carbonate/bicarbonate buffer pH 9·6 (200 μl) was incubated in ELISA plates (Nunc) at 4°C overnight. Plates were washed with phosphate buffered saline containing 0·05% Tween-20 (PBS-Tween). Doubling dilutions of test sera and of a pooled normal human serum were incubated in duplicate wells for 2 h at room temperature. The plates were washed and 200 μl of alkaline phosphatase labelled goat anti-human IgG (Miles UK, Ltd) appropriately diluted in PBS-Tween was incubated in all wells for 2 h at room temperature. The plates were washed and *p*-nitrophenyl phosphate disodium (Sigma, UK) diluted to 1 mg/ml in 10% diethanolamine buffer was added to all wells. Absorbance values were read at approximately 30 min

and the values for duplicates averaged. The highest dilution of test serum in which the absorbance value was above the background reading of the pooled normal human serum was recorded as the titre of anti-IgA antibodies.

*Serum immunoglobulins.* Serum concentrations of IgG, IgM and IgA were initially measured by automated immunoprecipitation using commercial antisera and standards, and in addition, IgA deficiency was confirmed by radial immunodiffusion using rabbit anti-IgA antiserum (Dako Ltd) and SPS-01 as standard.

*Statistics.* Statistical analyses were performed using a two-tailed Mann-Whitney *U*-test or $2 \times 2$ contingency table with Yate's correction.

## RESULTS

*Serum immunoglobulins.* Twenty-three of the 31 sera were deficient in IgA ($< 0{\cdot}05$ g/l); the other sera had degrees of partial IgA deficiency ranging from 0·06 to 0·4 g/l. Partial IgA deficiency was present in five patients with severe respiratory tract infections, two with mild infections and one patient without infections. IgG concentrations were normal or high in all sera and IgM concentrations were normal in all but two sera which had low IgM concentrations. Both sera with a low IgM were from patients with coeliac disease who did not have an increased susceptibility to infections. Because it was probable that the low IgM was related to the coeliac disease (Hobbs & Hepner 1966), both patients were included in the study.

*Serum IgG subclass concentrations.* Serum IgG subclass concentrations in the IgA-deficient patients and 95th centile ranges for healthy adult controls are shown in Fig. 1.

Statistical comparisons of IgG subclasses in the severe infection group with those in the group of patients with no increased susceptibility to infections revealed lower IgG2 concentrations ($P < 0{\cdot}02$), but no significant difference for the other subclasses.

Four of 11 (36%) patients with severe infections had IgG2 deficiency ($< 2{\cdot}5$th centile of the control group) but IgG2 concentrations were normal in all other patients. None of the IgG2-deficient sera were totally deficient.

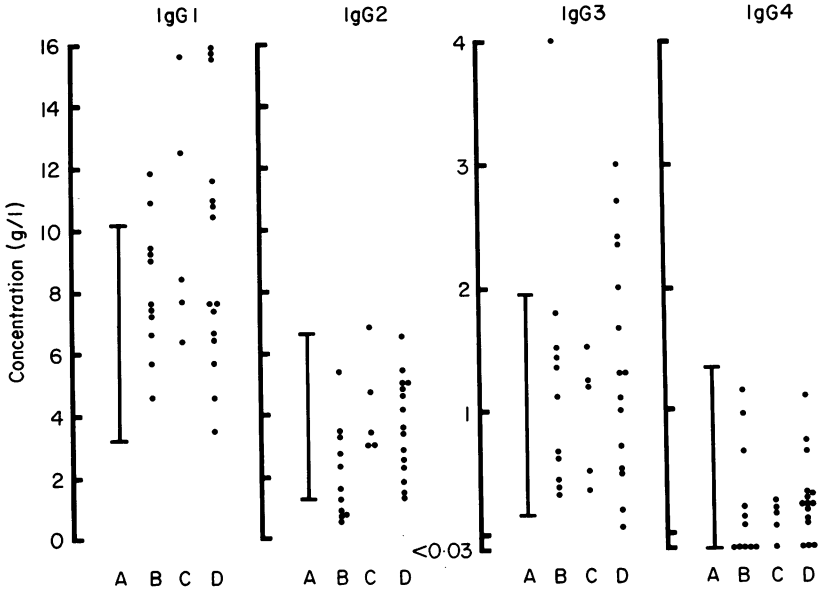


**Fig. 1.** Serum IgG subclass concentrations in healthy adult controls and IgA-deficient patients. A 95th centile range for controls ($n = 172$). B Severe respiratory tract infections ($n = 11$). C Mild respiratory tract infections ($n = 5$). D No increased susceptibility to respiratory tract infections ($n = 15$).

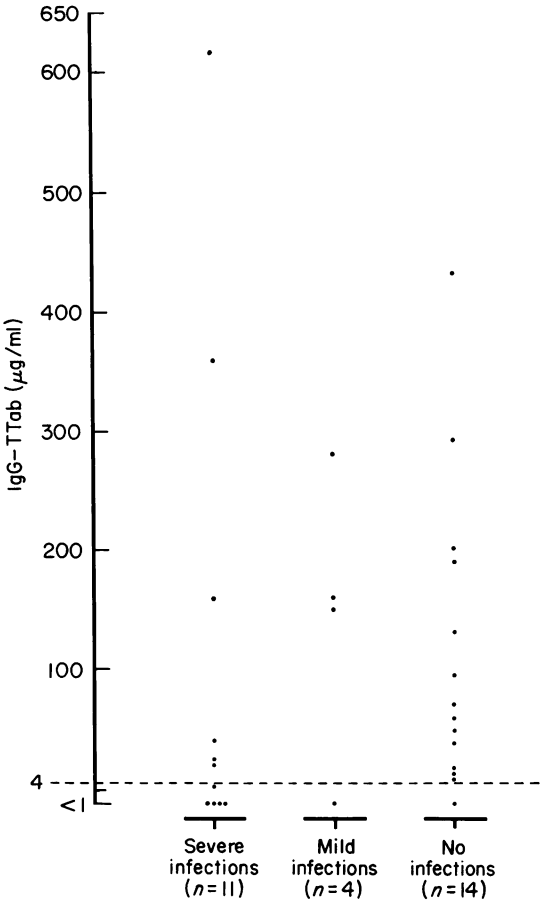


**Fig. 2.** Serum IgG-TTab concentrations following immunization in the three groups of IgA-deficient patients. A value of $<4$ μg/ml was determined to be subnormal from studies in healthy adults (see Methods).

It was not possible to determine whether any of the IgA-deficient sera were IgG4-deficient because the radial immunodiffusion assay did not have limits-of-detection low enough to detect IgG4 in all control sera. However, the number of sera in which IgG4 was not detected ($<0{\cdot}03$ g/l) was greater for IgA-deficient patients than controls; IgG4 was not detected in nine of 31 (29%) IgA-deficient sera compared with 17 of 172 (10%) control sera ($P<0{\cdot}01$). The association of IgA deficiency and undetectable IgG4 was particularly significant in patients with severe respiratory tract infections; IgG4 was not detected in five of 11 (45%) sera from patients with severe infections ($P<0{\cdot}01$) but only four of 20 (20%) sera from patients in the other two groups ($P>0{\cdot}05$). The larger number of sera with undetectable IgG4 from patients with severe infections can be explained by the effects of associated IgG2 deficiency; IgG4 was not detected in three of the four IgG2-deficient sera. When IgG2-deficient sera were excluded from analysis, IgG4 was not detected in the serum of two of 11 (18%) patients with severe infections, one of five (20%) with mild infections and three of 15 (20%) with no increased susceptibility to infections.

A single serum, from a patient without an increased susceptibility to infections, had a low IgG3 concentration (0·07 g/l) but no sera were deficient of IgG1. In contrast, several sera had high IgG1 or IgG3 concentrations ($>97{\cdot}5$th centile of the control group). Serum IgG1 concentrations were high in 11 of the 31 (35%) patients, predominantly those patients with mild infections or with no increased susceptibility to infections. Serum IgG3 concentrations were high in six of the 31 (19%) patients, all but one of whom had no increased susceptibility to infections.

**Table 1.** A comparison of the frequency of subnormal IgG-TTab responses and IgG subclass deficiency in the three groups of IgA-deficient patients

| Patient group | Subnormal IgG-TTab response | IgG2 deficiency | Undetectable IgG4 | One or more deficiency | Subnormal IgG-TTab response and/or IgG2 deficiency only |
|---|---|---|---|---|---|
| Severe infections ($n=11$) | 5 (45%) | 4 (36%) | 5 (45%) | 8 (73%) | 7 (64%) |
| Mild infections ($n=5$) | 1 of 4* (25%) | 0 | 1 (20%) | 2 (40%) | 1 (20%) |
| No infections ($n=15$) | 1 of 14* (7%) | 0 | 3 (20%) | 3 (20%) | 1 (7%) |

* Tetanus toxoid immunization not performed in one patient.

**Table 2.** Data on IgA-deficient patients with severe respiratory tract infections treated with gammaglobulin or plasma.

| | Serum immunoglobulins (g/l) | | | Serum IgG subclasses (g/l) | | | | IgG-TTab |
|---|---|---|---|---|---|---|---|---|
| Patient | G (5–16)* | M (0·5–2) | A (0·8–3) | 1 (3·2–10·2) | 2 (1·2–6·6) | 3 (0·16–1·9) | 4 (<0·03–1·3) | (μg/ml) (>4) |
| 1 | 8·8 | 1·9 | 0·06 | 7·60 | 0·85 | 1·43 | <0·03 | 2 |
| 2 | 13·2 | 0·6 | <0·05 | 11·90 | 1·25 | 0·61 | <0·03 | <1 |
| 3 | 10·1 | 1·2 | <0·05 | 7·25 | 0·55 | 1·80 | <0·03 | <1 |
| 4 | 10·3 | 0·7 | <0·05 | 6·60 | 2·30 | 0·44 | 0·06 | <1 |
| 5 | 10·4 | 1·4 | <0·05 | 9·0 | 0·72 | 1·51 | <0·03 | 25 |
| 6 | 11·0 | 1·3 | 0·06 | 10·9 | 0·75 | 0·67 | 0·12 | 614 |

* Reference ranges in healthy adults.

*Serum IgG-TTab concentrations following immunization.* Immunization studies were performed in 29 of the 31 patients. The IgG-TTab response was subnormal (< 4 μg/ml) in seven (29%) (Fig. 2). Five of these seven patients had severe respiratory tract infections; one had mild infections, but had had recurrent episodes of severe bronchitis as a child; the remaining patient had no abnormal susceptibility to infections.

*The frequency of IgG subclass deficiency and subnormal IgG-TTab responses in the different patient groups.* When considered together, IgG2 deficiency and/or a subnormal IgG-TTab response were particularly common in patients with severe respiratory tract infections (Table 1). If sera in which IgG4 was not detected are also included, the frequency of abnormalities is even greater for patients with severe respiratory tract infections, but this reduces the differences between the groups because of IgG4 was not detected in several sera from patients in the other two groups.

*Gammaglobulin treatment and its effect on anti-IgA antibody titres.* Five patients were treated with gammaglobulin therapy because of severe respiratory tract infections which were not adequately controlled with antibiotic therapy alone. *Haemophilus influenzae* was repeatedly cultured from the sputum of four of these five patients. All had IgG2 deficiency and/or a subnormal IgG-TTab response. Full details are shown in Table 2. The use of gammaglobulin therapy was associated with a reduction in the frequency and severity of respiratory tract infections in all five patients and there were no adverse effects. Anti-IgA antibodies were not detected in the serum of

three of the five patients before starting gammaglobulin therapy nor after at least 2 years of treatment. The serum of the other two patients contained anti-IgA antibodies in titres of 1/160 and 1/320 respectively, but neither titre increased after gammaglobulin therapy.

A further patient (No. 4 in Table 2) with repeated episodes of bronchitis and pneumonia and a subnormal IgG-TTab response was not treated with gammaglobulin because the serum contained anti-IgA antibodies at a titre of 1/20, 480 and there was a previous history of anaphylactoid reactions after blood transfusions. This patient was given infusions of IgA-deficient plasma, without adverse effect, but died before the effects of this could be adequately assessed.

## DISCUSSION

By demonstrating IgG2 deficiency and/or subnormal IgG-TTab responses, it has been shown that a proportion of IgA-deficient patients have defective IgG antibody responses in addition to IgA deficiency. Such defects were particularly common in patients with severe respiratory tract infections, suggesting that infection susceptibility was related to those defects, though some caution must be exercised in interpreting an analysis of several variables in a small number of patients.

Our findings confirm that IgG2 deficiency is present in a proportion of IgA-deficient patients with recurrent respiratory tract infections and that IgG2 concentrations are low but not absent (Oxelius *et al.*, 1981; Ugazio *et al.*, 1983; Stanley, Corbo & Cole, 1984). The significance of the IgG2 deficiency is not yet clear but may reflect defective antibody responses against polysaccharide antigens (Umetsu *et al.*, 1985). We have also shown that IgG4 is not detected in many IgA-deficient sera, particularly those with IgG2 deficiency. However, if IgG2 deficient sera are not considered, IgG4 was not detected in approximately 20% of all IgA-deficient sera irrespective of the patients' infection history. The significance of 'IgG4 deficiency' in IgA-deficient sera is, therefore, uncertain. Indeed, several studies have shown that IgG4 is not detected in up to 25% of sera from healthy individuals, presumably because of inadequate assay sensitivity (reviewed in French, 1986). However, using assay techniques with adequate sensitivity, IgG4 deficiency has been associated with an increased susceptibility to respiratory tract infections in IgA-deficient and non-IgA-deficient patients (Heiner, 1984). Until this issue has been clarified it seems prudent not to give gammaglobulin to IgA-deficient patients with IgG4 deficiency as an isolated additional defect.

The demonstration of subnormal IgG-TTab responses in a proportion of IgA-deficient patients is at variance with the conventional view that systemic antibody responses are normal in IgA deficiency (Ammann & Fudenberg, 1982). However, two other studies have demonstrated subnormal systemic antibody responses in some IgA-deficient individuals using other antigens. De Graeff *et al.* (1983) showed that both IgG and IgM antibody responses to the primary immunogen *Helix pomatia* haemocyanin were subnormal in some patients though, unlike this study, there was no direct relationship between subnormal responses and respiratory tract infections. Also, Umetsu *et al.* (1985) showed that IgA-deficient children with additional IgG2 deficiency had subnormal antibody responses to the capsular polysaccharide of *Haemophilus influenzae* type B. Our use of tetanus toxoid as a test antigen may even have underestimated the prevalence of subnormal systemic antibody responses in IgA-deficient patients, particularly in those with IgG2 deficiency, because tetanus toxoid does not induce an IgG2 antibody response in the great majority of individuals (French & Harrison, 1985).

It would appear, therefore, that there is a heterogeneity of antibody-mediated immune defects in selective IgA deficiency. Because it has been postulated that the B-lymphocyte defect in IgA deficiency is similar to, though less severe than, that in common variable hypogammaglobulinaemia (Cassidy, Oldham & Platts-Mills, 1979), IgA-deficient patients with IgG2 deficiency or subnormal systemic antibody responses may have a B-lymphocyte defect intermediate between that of common variable hypogammaglobulinaemia and asymptomatic IgA deficiency. It would, therefore, be of interest to determine if there are relationships between the severity of the B-lymphocyte defect, IgG subclass deficiency and subnormal systemic antibody responses.

Elevated serum concentrations of IgG1 and IgG3 presumably account for the high total IgG concentrations present in a proportion of IgA-deficient sera (Ammann & Hong, 1971; Koistinen,

1975). We have found high serum IgG1 and IgG3 concentrations to occur particularly in patients without an increased susceptibility to infections or with mild infections. Taken together with previous observations that total IgG is elevated more often in IgA-deficient sera from blood donors than hospital patients (Koistinen, 1975), these data support the opinion that IgG antibody responses are a compensatory factor in IgA-deficient individuals without an increased susceptibility to infections (Koistinen, 1975) and, furthermore, suggest that such antibody responses are predominantly IgG1 and IgG3.

The use of gammaglobulin therapy in IgA-deficient patients is a contentious issue (Buckley, 1985). It has been argued that it should not be given because firstly, it would not replace IgA and serum IgG concentrations are normal; and secondly, there is a potential risk that the small amounts of IgA in gammaglobulin could cause anaphylactoid reactions in those patients with anti-IgA antibodies, or induce anti-IgA antibodies if not already present. However, gammaglobulin therapy has been used in IgA-deficient patients without adverse effects (Van der Giessen *et al.*, 1976; Koistinen *et al.*, 1978; Bjorkander *et al.*, 1985).

It is clear that some IgA-deficient patients also have defects of IgG, and it would appear that the long-term effects of repeated respiratory tract infections in such individuals will be structural lung damage (Bjorkander *et al.*, 1985). Gammaglobulin therapy might prevent this. In this study, gammaglobulin was given to a small number of carefully selected patients whose infections were inadequately controlled by antibiotics. There were no adverse reactions and anti-IgA antibody production was not induced. It appeared that this therapy was effective, but a formal trial on a much larger number of patients is required to determine whether gammaglobulin therapy is truly efficacious in such patients.

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