CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY 13, 182–186 (1979)

Antibodies to Nucleic Acid Antigens in Selective IgA Deficiency

R. E. PETTY,* M. HADDOW,* K. OEN,* W. BEES,* J. T. CASSIDY,† AND D. G. TUBERGEN‡

** Department of Pediatrics and the Rheumatic Diseases Unit, University of Manitoba, Winnipeg, Manitoba; † Departments of Pediatrics and Medicine, University of Michigan, Ann Arbor, Michigan 48104; and ‡ Department of Oncology, Denver Children's Hospital and University of Colorado, Denver, Colorado 80218*

Received December 19, 1978

Antibodies to nucleic acid antigens were measured in symptomatic and asymptomatic IgA-deficient individuals, non-IgA-deficient blood donors, and patients with systemic lupus erythematosus (SLE). There was no increase in mean levels of antibodies to nucleic acid antigens (native or denatured DNA, transfer RNA) in the IgA-deficient group, although 4 of 100 IgA-deficient blood donors had persistently increased levels of antibody to native DNA. IgA deficiency has been previously shown to be associated with SLE, but there does not appear to be an intrinsic association between IgA deficiency and antibodies to nucleic acid antigens.

INTRODUCTION

The demonstration of an increased prevalence of selective IgA deficiency (SIgAD) in systemic lupus erythematosus (SLE) (1) and a report of an increased frequency of antibody to DNA in immune deficiency (2) prompted study of the frequency of antibodies to native and denatured DNA, to single-stranded RNA, and to other nuclear antigens in a large group of individuals with SIgAD.

MATERIALS AND METHODS

Study Groups

The individuals with SIgAD all had serum IgA levels <0.01 mg/ml as determined by radial diffusion in gel (3). Of 21 symptomatic patients, 8 had juvenile rheumatoid arthritis or ankylosing spondylitis, 7 recurrent upper respiratory tract infections, 3 malabsorption syndromes, 1 thyroiditis, 1 dermatomyositis, and 1 Gaucher's disease. Sera from SIgAD blood donors were obtained from the Blood Transfusion Service of the Canadian Red Cross in Winnipeg. Non-IgA-deficient blood donors and patients with SLE but normal or elevated levels of IgA were included for comparison.

Preparation of Radioiodinated Antigens

Calf thymus DNA (Sigma) or transfer RNA (tRNA) were labeled with ^{125}I by the thallium trichloride method (4). Double-stranded ^{125}I-labeled DNA (dsDNA) was then isolated by passage through a hydroxyl apatite column (5). Only DNA preparations having <2% cleavage by S1 nuclease were used (6). Denatured DNA was prepared by heating the dsDNA to 100°C for 15 min and cooling it rapidly on ice. tRNA was isolated by thermal elution from hydroxyl apatite (7).

0090-1229/79/060182-05$01.00/0

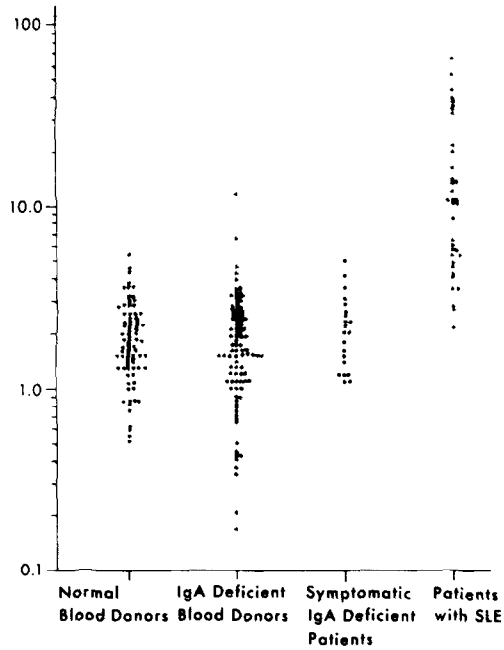

FIG. 1. Antibody to dsDNA (% binding) in control and IgA-deficient groups.

Quantitation of Antibody Reactive with Nucleic Acid Antigens

Anti-DNA antibodies were quantitated in triplicate by an ammonium sulfate precipitation technique previously described (8). The results were expressed as percentage binding of 0.26 μg ^{125}I-labeled DNA by 15 μl of serum. Anti-tRNA antibodies were measured in duplicate by an ammonium sulfate precipitation technique: 0.20 μg of ^{125}I-labeled tRNA was incubated with 60 μl of serum for 1 hr at room temperature. The assay was otherwise performed as described for anti-DNA (8). Antinuclear antibodies in undiluted serum were demonstrated by immunofluorescence (F-ANA) using mouse liver substrate as previously described (9).

RESULTS

Antibodies to dsDNA

The values for percentage binding in the control and SIgAD groups are shown in Fig. 1. Binding in the control group (n = 83) was 1.96 ± 0.95% (mean ± 1 SD), range 0.52 to 5.4%. In patients with SLE, but with normal or increased levels of IgA (n = 36), binding ranged from 2.1 to 64.3% (15.9 ± 15.5). In the group with SIgAD as a whole (n = 121), the range of binding was 0.17 to 11.6%. Of the symptomatic patients with SIgAD, one had anti-dsDNA levels beyond 2 SD of the normal mean. Of 100 blood donors with SIgAD, 4 had elevation of DNA binding beyond 2 SD of the normal mean. Second samples, obtained 3 to 6 months after the initial samples, and medical histories were obtained from each of these donors. The high values of DNA binding persisted in sequential samples. None of the donors had symptoms suggestive of SLE. None had positive tests for rheumatoid factors or Coombs' antibody. Although initial sera did not have demonstrable

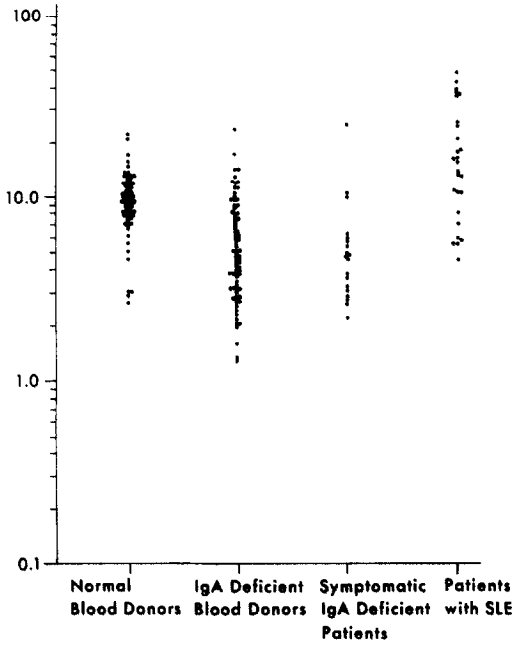

FIG. 2. Antibody to heat-denatured DNA (% binding) in control and IgA-deficient groups.

F-ANA, such antibodies were demonstrated in second samples from 2 donors with the highest binding to dsDNA.

Antibodies to Denatured DNA

The mean percentage binding of denatured DNA in SIgAD donors (5.99 ± 3.76%, n = 89) was lower than that in normal donors (9.66 ± 3.1%, n = 90) (Fig. 2). Elevated levels were found in 12 patients with SLE and in one IgA-deficient donor who also had elevated antibody to dsDNA.

Antibodies to tRNA

Values in the control group (n = 83) showed tRNA binding of from 1.62 to 6.76% (3.7 ± 2.45). In non-IgA-deficient patients with SLE (n = 23), binding ranged from 1.43 to 13.74% (7.17 ± 2.50). In the asymptomatic IgA-deficient blood donors (n = 65) values ranged from 0.16 to 11.65% (4.62 ± 1.98).

Antinuclear Antibodies

F-ANA were detected in 3 of 100 IgA-deficient blood donors and in none of the 83 normal blood donors.

DISCUSSION

The overall frequency of F-ANA and elevated levels of binding to native or denatured DNA or to transfer RNA were not significantly different in IgA-deficient and non-IgA-deficient blood donor populations. However, four IgA-deficient donors were found to have persistently increased levels of antibody to dsDNA (>2 SD normal mean), although there was no evidence of autoimmune

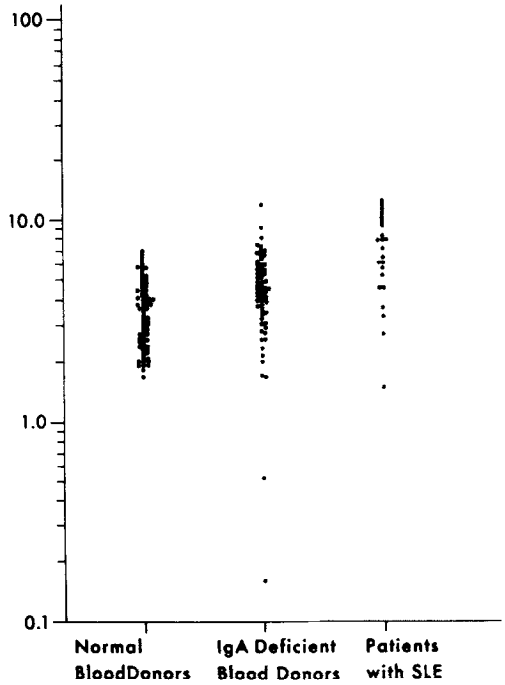

FIG. 3. Antibody to transfer RNA (% binding) in control and IgA-deficient groups.

disease. Further follow-up will be necessary in order to evaluate the possibility that these donors are developing SLE.

We conclude from these data that there is no intrinsic association between SIgAD and increased levels of antibody to nuclear antigens, and that any apparent association is attributable to an underlying autoimmune disease (SLE) rather than to SIgAD per se. This conclusion contrasts with that of Gershwin *et al.* (2) who noted an association between SIgAD and antibodies to nucleic acids. Of 37 IgA-deficient patients whom they reported, 6 had antibodies to dsDNA, 7 to ssDNA, and 4 to dsRNA. Of the 11 patients who had antibodies to at least one nucleic acid antigen, 5 were asymptomatic, 2 had rheumatoid arthritis, and 1 each had Hodgkin's disease, juvenile rheumatoid arthritis, recurrent infections, and antibody to Factor XI. No patient was thought to have SLE. Their study and ours differ with respect to criteria for designation of SIgAD, techniques used to assay antibodies, and patient and donor origins. Such differences may contribute to the apparent disparity between the reported results and conclusions.

ACKNOWLEDGMENTS

The support of the Manitoba Medical Services Foundation Inc. and the Canadian Arthritis Society and the cooperation of the Blood Transfusion Service of the Canadian Red Cross, Winnipeg, are gratefully acknowledged.

REFERENCES

1. Cassidy, J. T., Burt, A., Petty, R. E., and Sullivan, D. B., *N. Engl. J. Med.* **280**, 275, 1970.

2. Gershwin, M. E., Blaese, R. M., Steinberg, A. D., Wistar, R., and Strober, W., *J. Pediat.* **89**, 377, 1976.
3. Cassidy, J. T., Petty, R. E., and Sullivan, D. B., *J. Clin. Invest.* **52**, 1931, 1973.
4. Commerford, S. L., *Biochemistry* **10**, 1933, 1971.
5. Meinke, W., Goldstein, D. A., and Hall, M. R., *Anal. Biochem.* **58**, 82, 1974.
6. Vogt, V. M., *Eur. J. Biochem.* **33**, 192, 1973.
7. Kalmakoff, J., and Payne, C. C., *Anal. Biochem.* **55**, 26, 1973.
8. Cassidy, J. T., Walker, S. E., Soderstrom, S. J., Petty, R. E., and Sullivan, D. B., *J. Pediat.* **93**, 414, 1978.
9. Petty, R. E., Cassidy, J. T., and Sullivan, D. B., *J. Pediat.* **83**, 386, 1973.