Acta Derm Venereol (Stockh) 1995; 75: 130–132

Selective Increase of IgA Rheumatoid Factor in Patients with Gluten Sensitivity

MARTIN SÖKJER, THORBJÖRN JÓNSSON, SIGURDUR BÖDVARSSON, INGILEIF JÓNSDÓTTIR and HELGI VALDIMARSSON

Department of Immunology, National University Hospital, Landspítalinn, Reykjavík, Iceland

An increased prevalence of raised autoantibodies, including rheumatoid factor, has been reported in patients with gluten sensitivity. However, rheumatoid factor has only been measured in small groups of patients and the findings have been conflicting. In this study IgM, IgG and IgA rheumatoid factor was measured in 89 patients with dermatitis herpetiformis and 22 patients with coeliac disease and compared with 89 normal controls. There was an increased prevalence of elevated IgA rheumatoid factor in the patients with dermatitis herpetiformis (13.5%; $p = 0.036$) and coeliac disease (18.2%; $p = 0.078$), while no such increase was found for the IgM or IgG rheumatoid factor isotypes. This selective increase of IgA rheumatoid factor suggests that rheumatoid factor production in patients with gluten sensitivity primarily results from immunological activation in the gut mucosa. ***Key words: dermatitis herpetiformis; coeliac disease; autoantibodies.***

(Accepted September 9, 1994.)

Acta Derm Venereol (Stockh) 1995; 75: 130–132.

H. Valdimarsson, Department of Immunology, National University Hospital, Landspítalinn, ÍS-101 Reykjavík, Iceland.

IgA antibodies may be of pathogenic significance in dermatitis herpetiformis (DH) but probably not in coeliac disease (CD). IgA-containing circulating immune complexes have been reported both in DH and CD patients (1), but deposits of IgA antibodies are only found in the papillary dermis of uninvolved skin in DH but not in CD patients (2). It has not been possible to elute functional IgA antibodies from DH skin and their specificity is therefore not known. However, the IgA deposits gradually disappear in patients on gluten-free diet, suggesting that the IgA in the skin of DH patients originates from an immune response to component(s) of gluten in the gut (3). Raised levels of various autoantibodies have also been reported both in DH and CD patients, including antibodies against thyroid antigens (4–7), endomysium (8), reticulin (8), parietal cells (4, 9), nuclear antigens (9) and IgG (rheumatoid factor, RF) (10–12). In contrast, DH patients have been found to have lower levels of IgA antibodies to high molecular weight glutenin and human elastin than both normal controls and CD patients (13). The reduction of IgA elastin antibodies was more pronounced in patients on gluten-free diet, and it was therefore proposed that glutenin antibodies which cross-react with human elastin may accumulate in the skin of DH patients and thereby be depleted from the circulating pool (13). However, analysis of autoantibody isotypes has generally not been made in patients with gluten sensitivity, and it is therefore not known whether low levels of autoantibodies of the IgA isotype constitute a general phenomenon in DH. In this paper we report a preferential increase of IgA RF in patients with DH and CD.

MATERIALS AND METHODS

Patients and samples

Altogether 200 samples of serum were measured for IgM, IgG, and IgA RF. Of these 63 were from DH patients on a gluten-free diet, 26 from DH patients on a normal diet and 22 from CD patients. DH patients were considered to adhere strictly to gluten-free diet if they were symptom free without dapsone treatment and their gliadin antibodies were not raised.

Samples from 89 randomly selected healthy adults, aged 31–50 years, were used as controls. The DH and control samples had all previously been measured for IgG and IgA antibodies against gliadin, high molecular weight glutenin, human aortic elastin (13) and also for antibodies to various food antigens (manuscript in preparation).

Measurement of RF

RF isotypes were measured by a modified ELISA system, which has been described in detail elsewhere (14). Briefly, Dynatech Immunolon I plates were coated over night at 4°C with a 40 µg/ml solution of purified rabbit IgG (Sigma). Dilutions of the serum samples were incubated for 3 h at room temperature. The IgG and IgM RF isotypes were detected with alkaline phosphatase (AP)-coupled mouse monoclonal anti-human IgM (Sigma, clone MB-11) and anti-human IgG (Sigma, clone GG-5) antibodies. IgA RF was detected with a mouse monoclonal anti-human IgA antibody (Oxoid, clone 2D7 M26) incubated at 4°C over night, followed by AP-coupled, rabbit anti-mouse antibody (Dakopatts). All AP-coupled detector antibodies were incubated for 2 h at room temperature. Finally a 10 mg/ml p-nitrophenyl phosphate substrate solution was added and the absorbance read at 405 nm in a Titertek Multiscan (Flow Laboratories) when absorbance of the strongest standard dilution had reached 1.5–1.8. Results were expressed in arbitrary units (AU/ml) according to serial dilutions of a local standard prepared from sera collected from 11 patients with rheumatoid arthritis (RA) and high levels of all RF isotypes. The upper limit of normal for the RF isotypes was set at the 95% cutoff level for the control group. The interassay variability was found to be 16% and the intraassay variability 14%. The detection limit was 10 AU/ml for IgM RF, 6 AU/ml for IgG RF and 6 AU/ml for IgA RF. In this ELISA assay system approximately 90% of RA patients have elevated levels of one or more RF isotypes (IgM RF in 70%, IgG RF in 45% and IgA RF in 60% of RA patients).

Statistical analysis

For evaluation of the results the chi-square test (with Yates correction for expected frequencies less than five), the Mann-Whitney U-test and Spearman rank correlation coefficient were used. The level of significance was set at $p < 0.05$.

RESULTS

Of the DH patients 12 (13.5%) had elevated levels of IgA RF (Fig. 1, $p = 0.036$). No difference in IgA RF levels was observed between DH patients on gluten-free diet and DH patients on normal diet (Fig. 2, $p = 0.181$). Patients with CD also tended to have raised levels of IgA RF (18.2%; $p = 0.078$). In contrast, no increase was found in IgM RF and IgG RF in the DH or CD patients.

 ISSN 0001-5555

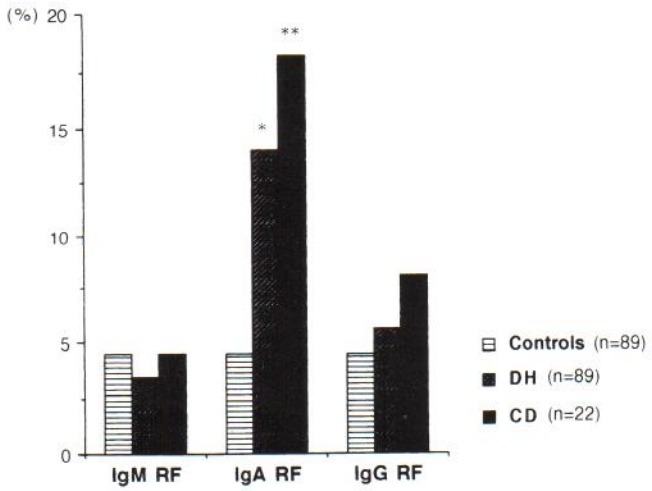

Fig. 1. Prevalence of elevated IgM, IgA and IgG REF in controls and patients with dermatitis herpetiformis (DH) and coeliac disease (CD). Significance as compared with the control group: * $p=0.036$, ** $p=0.078$.

As shown in Table I, the DH patients had significantly lower levels of IgA antibodies to both elastin and glutenin than both the controls and the CD patients. No difference was found in IgA antibodies to glutenin or elastin between the IgA RF positive and negative DH patients (Table I). Patients with low levels of IgA antibodies against glutenin and elastin did not have lower IgA RF, and the IgA RF was not reduced in patients on gluten-free diet (data not shown).

When all detectable RF levels were analysed, a significant positive correlation was found between IgM and IgA RF and between IgG and IgA RF, but not between IgM and IgG RF, both in the controls and the patients.

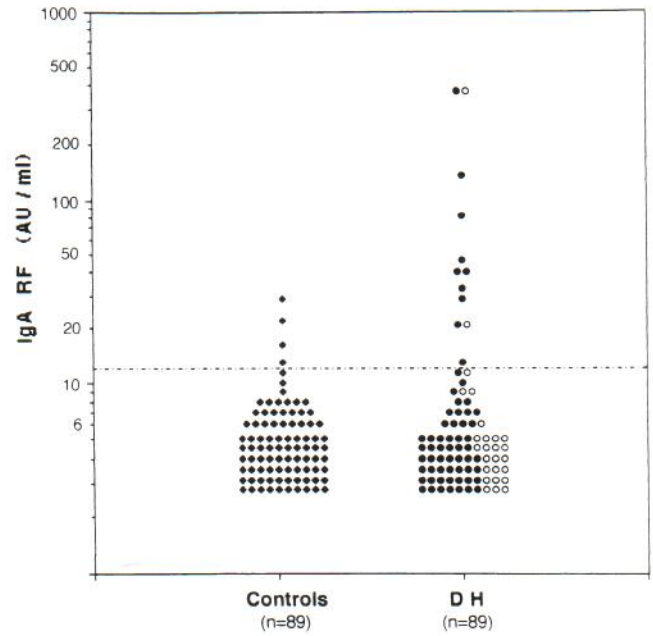

Fig. 2. Levels of IgA RF in 63 dermatitis herpetiformis (DH) patients on gluten-free diet (●), 26 dermatitis herpetiformis patients on normal diet (○) and in the 89 control subjects. The dotted line indicates the upper limit of normal for IgA RF.

Table I. *Comparison of IgA antibody levels (median) to elastin and glutenin in controls, CD patients and DH patients with elevated and normal levels of IgA RF*

	IgA antibodies to:	
	Elastin	Glutenin
DH patients with elevated IgA RF (n=12)	17.0[a]	17.8
DH patients with normal IgA RF (n=77)	21.0	14.8
CD patients (n=22)	45.0**	30.0*
Controls (n=89)	39.0**	21.0*

[a] Median antibody level (AU/ml) in each group.
Significance as compared with all the 89 DH patients:
*$p<0.05$ **$p<0.0001$.

DISCUSSION

In this paper we report a selective increase in the prevalence of raised IgA RF in patients with gluten sensitivity. It has previously been claimed that IgM RF, IgG RF and IgA RF are all elevated in DH patients (10), while others have only reported elevation of IgM RF (11). To our knowledge no information is available about the RF isotypes in patients with CD. In agreement with the finding that IgA RF can persist for many years in symptom-free individuals (15, 16), DH patients on gluten-free diet did not have lower IgA RF than patients on normal diet. This contrasts with the observation that IgA antibodies to human elastin are reduced in DH patients, particularly those on gluten free diet (13) and supports the notion that IgA elastin antibodies may be selectively taken up by microfibrillar elastin components in the skin of DH patients (17).

The observation that a correlation exists between IgM RF and IgA RF and between IgG RF and IgA RF, but not between IgM RF and IgG RF, is in agreement with previous findings for patients with rheumatic disorders (16).

It has been reported that patients with Sjögren's syndrome and other symptoms originating from mucous membranes tend to have isolated or preferential increase in IgA RF (18, 19). Our finding of an increased prevalence of raised IgA RF, but not IgM RF or IgG RF, in patients with gluten sensitivity is therefore likely to reflect an increased immunological activity in the gut mucosa.

Increased incidence of intestinal lymphoma has been noted in patients with CD (20, 21) and also in DH (22, 23), although strict adherence to gluten-free diet may reduce the risk of developing malignancy (23–25). We have previously shown that elevated levels of IgA RF in non-rheumatic individuals, but not other RF isotypes, are associated with increased incidence of cancer (15). Thus, elevation of IgA RF in patients with gluten sensitivity may reflect an excessive stimulation or activity of the immune system at mucosal level, which may eventually lead to malignancy.

REFERENCES

1. Hall RP, Strober W, Katz SI, Lawley TJ. IgA circulating immune complexes in gluten-sensitive enteropathy. Clin Exp Immunol 1981; 45: 234–235.
2. Seah PP, Fry L, Stewart JS, Chapman BL, Hoffbrand AV, Holborow

EJ. Immunoglobulins in the skin in dermatitis herpetiformis and coeliac disease. Lancet 1972; I: 611–614.
3. Hall RP. The pathogenesis of dermatitis herpetiformis: recent advances. J Am Acad Dermatol 1987; 16: 1129–1144.
4. Frazer NG. Autoantibodies in dermatitis herpetiformis. Br J Dermatol 1970; 83: 609–612.
5. Cunningham MJ, Zone JJ. Thyroid abnormalities in dermatitis herpetiformis. Prevalence of clinical thyroid disease and thyroid autoantibodies. Ann Intern Med 1985; 102: 194–196.
6. Gaspari AA, Huang CM, Davey RJ, Bondy C, Lawley TJ, Katz SI. Prevalence of thyroid abnormalities in patients with dermatitis herpetiformis and in control subjects with HLA-B8/-DR3. Am J Med 1990; 88: 145–150.
7. Weetman AP, Burrin JM, MacKay D, Leonard JN, Griffiths CE, Fry L. The prevalence of thyroid autoantibodies in dermatitis herpetiformis. Br J Dermatol 1988; 118: 377–383.
8. Hallstrom O. Comparison of IgA-class reticulin and endomysium antibodies in coeliac disease and dermatitis herpetiformis. Gut 1989; 30: 1225–1232.
9. Hoffbrand AV, Holborow EJ, Seah PP, Fry L. Tissue antibodies in dermatitis herpetiformis and adult coeliac disease. Lancet 1971; I: 834–836.
10. March RE, Kirwan JR, Davies PG, Winrow VR, Holborow EJ. Sensitive ELISA measurements of IgA, IgG and IgM antiglobulins in rheumatic and other diseases and a comparison of their specificity in rheumatoid atthritis and infectious mononucleosis. Scand J Rheumatol 1987; 16: 445–449.
11. Hall RP, Eyre RW. IgA immune complexes in patients with dermatitis herpetiformis occur in absence of IgA rheumatoid factor. J Invest Dermatol 1987; 89: 27–31.
12. Kalimo K. Rheumatoid factor in sera of dermatitis herpetiformis patients. Br J Dermatol 1978; 78: 79–83.
13. Bödvarsson S, Jónsdóttir I, Freysdóttir J, Leonard JN, Fry L, Valdimarsson H. Dermatitis herpetiformis – an autoimmunodisease due to cross-reaction between dietary glutenin and dermal elastin? Scand J Immunol 1993; 38: 546–550.
14. Jónsson T, Arnason JA, Valdimarsson H. Enzyme-linked immunosorbent assay (ELISA) screening test for detection of rheumatoid factor. Rheumatol Int 1986; 6: 199–204.
15. Jónsson T, Thorsteinsson J, Valdimarsson H. Rheumatoid factor isotypes and cancer prognosis. Cancer 1992; 69: 2160–2165.
16. Jónsson T, Thorsteinsson J, Kolbeinsson A, Jónasóttir E, Sigfússon N, Valdimarsson H. Population study of the importance of rheumatoid factor isotypes in adults. Ann Rheum Dis 1992; 51: 863–868.
17. Reunala T, Rantala I, Pihlman K, Linder E. Microfibrils of elastic fibres as a major site of IgA deposition in dermatitis herpetiformis: an immunofluorescence and immunoelectron microscopical study. In: MacDonald DM, ed. Immunodermatology. London: Bulterworth & Co., 1984: 237–239.
18. Elkon KB, Gharavi AE, Patel BM, Hughes GRV, Frankel A. IgA and IgM rheumatoid factors in serum, saliva and other secretions: relationship to immunoglobulin ratios in systemic sicca syndrome and rheumatoid arthritis. Clin Exp Immunol 1983; 52: 75–84.
19. Lúdvíksson BR, Jónsson T, Erlendsson K, Sigfússon A. Disease manifestations in patients with isolated elevation of IgA rheumatoid factor. Scand J Rheumatol 1992; 21: 1–4.
20. Swinson CM, Slavin G, Coles EC, Booth CC. Coeliac disease and malignancy. Lancet 1983; I: 111–115.
21. Holmes GKT, Stokes PL, Sorahan TM, Prior P, Waterhouse JAH, Cooke WT. Coeliac disease, gluten-free diet, and malignancy. Gut 1976; 17: 612–619.
22. Gawkrodger DJ, Barnetson RSTC. Dermatitis herpetiformis and lymphoma. Lancet 1982; II: 987.
23. Leonard JN, Tucker WFG, Fry JS, Coulter CAE, Boylston AW, McMinn RMH, et al. Increased incidence of malignancy in dermatitis herpetiformis. BMJ 1983; 286: 16–18.
24. Reunala T, Hakala T, Helin H. Dermatitis herpetiformis, lymphoma, and gluten-free diet. J Am Acad Dermatol 1984; 10: 526–527.
25. Holmes GKT, Prior P, Lane MR, Pope D, Allan RN. Malignancy in coeliac disease – effect of a gluten free diet. Gut 1989; 30: 333–338.