ANTIGLIADIN ANTIBODIES IN DERMATITIS HERPETIFORMIS

by

S. A. McMILLAN, THELMA HUTCHISON, MARGARET HAIRE, GRACE ALLEN and AGNESE KELLY

Immunology Laboratory and Skin Department, Belfast City Hospital

DERMATITIS herpetiformis (DH) is an intensely itchy dermatosis of a chronic nature. Although the lesions most often consist of tense vesicles grouped on the extensor surfaces of the body, they may also be erythematous, urticarial or papular and more diffuse. As a result of the intense itch the lesions are excoriated and frequently present as small crusted areas. Thus other parameters are necessary to assist in diagnosis.

For many years therapeutic response to sulphones or sulfrapyridine was an important criterion in diagnosis, while more recently the diagnosis has been confirmed by the finding of deposits of immunoglobulin A (IgA) in clinically uninvolved skin. Since gluten sensitive enteropathy occurs in all patients with DH in varying degrees,[1] associated villous atrophy in jejunal biopsies has been used as an additional diagnostic aid. The presence of a serum antibody to gliadin, a component of gluten, has been associated with patients with gluten sensitive enteropathy,[2, 3] and we suggest that detection of this antibody may be an additional help in differentiating patients with DH from patients with other itchy skin conditions and may in certain cases eliminate the need for a jejunal biopsy sample.

PATIENTS AND METHODS

Patients

During the period April 1976 to December 1980, one hundred and thirty patients presented at the Skin Department, Belfast City Hospital, with an itchy skin rash. The age of these patients ranged from 9 years to 86 years with a sex distribution of 70F:60M. Serum and skin biopsy samples were obtained from all the patients for routine autoantibody screening and immunopathology. The final diagnosis of the 130 patients was based on clinical features and immunopathology. A diagnosis of DH was based on the clinical appearance of the rash, the response to dapsone, and the presence of IgA deposits in uninvolved skin. All patients at the time of sampling were on a normal diet and not on dapsone therapy.

Biopsy Specimens

Eliptical skin biopsies, excised with a scalpel from uninvolved areas of skin under local anaesthetic, were obtained from all 130 patients and were snap frozen in liquid nitrogen. Jejunal biopsies were obtained from 20/130 patients.

Immunopathology and Histopathology

Cryostat sections (5 μm thick) were tested by direct immunofluorescence using fluorescein isothiocyanate (FITC) conjugated sheep antibodies to human IgG, IgA,

IgM, C_3 and fibrinogen (Wellcome Diagnostics, England). Jejunal biopsies were stained by haematoxylin and eosin.

Serological Investigations

The sera of the 130 patients were tested for autoantibodies in the IgG, IgA and IgM classes to nuclei, smooth muscle, gastric parietal cells, mitochondria, thyroid, reticulin and gliadin.[4] Sera were only considered positive for antireticulin antibody (ARA) if the R1 fluorescence pattern described by Rizzetto and Doniach[5] was seen. IgG, IgA and IgM class antigliadin antibodies were detected by indirect immunofluorescence, as described by Unsworth et al.[6] Serum samples were tested on cryostat sections of rat composite tissues which had been exposed at room temperature to an aqueous solution of gliadin (Sigma Chemical Company) (0.1 mg/ml). The sections were first exposed to the patients' sera and after washing in phosphate buffered saline (PBS) for 30 minutes, they were exposed to FITC-conjugated sheep antihuman IgG, antihuman IgA and antihuman IgM (Wellcome Diagnostics, England) for a further 30 minutes. After a further hour's wash, the slides were mounted in glycerol saline, and were examined with a Leitz immunofluorescent microscope. Those sera with antigliadin activity gave a reticulin pattern similar to that of the R1 fluorescent staining of ARA on rat composite tissues not pre-treated with gliadin.

RESULTS

Clinical categories

The final clinical assessment of the 130 patients who presented with an itchy skin is as follows: Prurigo was the most common diagnosis (42/130 patients). Dermatitis herpetiformis was diagnosed in 26/130 patients and in a further five patients a diagnosis of DH was thought probable as these patients responded clinically to dapsone. However, IgA deposits were not detected in biopsies of their uninvolved skin, and repeat biopsies were not performed. Eczema was the third most common diagnosis (19/130). Four patients had dermatitis, three each urticaria or pemphigoid, two each nickel sensitivity or neurodermatitis. There was also one case each of bullous eruption, myeloid metaplasia, subcorneal pustular dermatosis, vasculitis, pityriasis lichenoides et varioliformis acuta and acne excoree. A diagnosis was not made in 15 patients.

Skin immunopathology

In 23/26 patients, whose uninvolved skin contained IgA deposits, the pattern was papillary while in the remaining three, it was linear in character. Sometimes deposits of IgM and C_3 were also found.

Villous atrophy

Jejunal biopsies were performed in 16 of the 26 patients with DH. There was significant villous atrophy of the jejunal mucosa in 11/16 of these patients and in 8 of these 11 patients AGA was found. Anti-gliadin antibody was not found in the five patients with DH with normal jejunal mucosa, nor in the group of patients without deposits of IgA in skin (probable DH) (Table). Normal mucosa was found in jejunal biopsy specimens in 4/5 of these patients.

TABLE

Titres of antibodies to gliadin and to reticulin in immunoglobulin classes G and A and findings of histopathological examination of jejunal biopsies in the 26 patients with DH.

Patient Number	*Titre[a] of antibody to gliadin*		*Titre[a] of antibody to reticulin*		*Jejunal Villous atrophy*
	IgG	*IgA*	*IgG*	*IgA*	
1	20	—	—	—	ND[b]
2	—	80	—	80	+
3	20	20	20	20	ND
4	40	20	40	—	+
5	—	40	—	—	+
6	20	—	—	—	+
7	—	20	—	—	+
8	80	20	—	—	ND
9	20	—	—	—	+
10	20	20	—	—	ND
11	20	—	—	—	+
12	—	40	—	—	+
13	—	320	—	320	ND
14	—	—	—	—	+
15	—	—	—	—	+
16	—	—	—	—	+
17	—	—	—	—	ND
18	—	—	—	—	—
19	—	—	—	—	—
20	—	—	—	—	ND
21	—	—	—	—	ND
22	—	—	—	—	—
23	—	—	—	—	—
24	—	—	—	—	—
25	—	—	—	—	ND
26	—	—	—	—	ND

a Antibody titre is expressed as a reciprocal of the serum dilution.

b Not done.

Serological findings

The sera of 13/130 patients contained antibody to gliadin in IgG and IgA classes only, and these patients were all diagnosed as DH. Five patients had AGA in IgA class; four patients AGA in IgG class and four patients had AGA in both IgA and IgG classes. In only four of the AGA positive patients was there a corresponding presence of antireticulin R1 antibody (Table). Other autoantibodies detected were not of significance.

DISCUSSION

The variety of skin conditions which present with an itchy skin indicates the need for simple tests to help in diagnosis. We present evidence that the presence of AGA in serum may be an additional screening test defining patients with DH in whom there is marked enteropathy. Antigliadin antibody has been detected in a number of patients with DH and coeliac disease and its presence is a good indicator of the degree of gluten sensitivity as expressed by mucosal damage.[2, 3]

In the present study detection of AGA in serum of 50 per cent (13/26) of the patients in whom DH was diagnosed, and the correlation between the presence of this antibody and atrophy of the jejunal mucosa is in agreement with the findings of Unsworth and his colleagues.[2] In all of our patients with AGA, from whom jejunal biopsies were obtained, villous atrophy was found.

In the five patients who were diagnosed as "probable" DH, IgA deposits were not found in uninvolved skin, although they did have a characteristic skin rash which responded to dapsone. Fry and Seah[7] have stated that more than one biopsy may be needed if IgA deposits are to be found. It is interesting to note that neither AGA nor ARA was detected in these patients, and in those from whom jejunal biopsies were obtained, the mucosa was normal.

Antigladin antibodies are not specific for patients with DH and they have been reported in a percentage of patients with other intestinal conditions such as coeliac disease, transient gluten intolerance, cow's milk sensitive enteropathy, Crohn's disease and ulcerative colitis.[3, 6, 8] In our series AGA was only found in those patients with DH and this is probably due to the fact that none of the other patients had clinical evidence of intestinal disease.

Antigliadin antibody in the IgA class has been reported to be a sensitive indicator of severe gluten sensitivity in patients with coeliac disease, and appears to be most likely to be found in this condition.[3] However, in patients with DH we have found AGA in both IgG and IgA classes in association with villous atrophy.

In this investigation, AGA were only found in patients with DH who had associated atrophy of their jejunal mucosa, and therefore the presence of AGA may be a useful additional test for the diagnosis of patients with DH who have marked gluten enteropathy and may eliminate the need for a jejunal biopsy in these patients. The presence of AGA may also be useful to monitor the effectiveness of a gluten-free diet in patients with DH.

SUMMARY

During the period April 1976 to December 1980, 130 patients presented at the Skin Department, Belfast City Hospital, complaining of an itchy dermatosis suggestive of dermatitis herpetiformis. Twenty-six of these patients were finally diagnosed as having dermatitis herpetiformis (DH) on the basis of the response of the rash to dapsone and the presence of IgA deposits in uninvolved skin. Antibodies to gliadin (AGA) were detected in 13 of these patients and in those patients from whom a jejunal biopsy was taken, the presence of AGA correlated with villous atrophy. We report that the presence of AGA may be of additional help in the diagnosis of DH and may, in certain cases, eliminate the need for jejunal biopsy.

We wish to thank the medical and nursing staff of the Skin Department and Gastroenterology Unit, Belfast City Hospital and also the staff of the Immunology Laboratory, Belfast City Hospital for their technical assistance. We would also like to thank members of the Histopathology Department, Belfast City Hospital for examination of the jejunal biopsies. We thank Mrs. J. Hamill who typed the manuscript.

REFERENCES

1 Fry L. In *Immunopathy of the Skin.* 2nd Edn. (edited by EH Beutner, TP Chlorzelski and SF Bean) Chap 13. London: Wiley Medical 1979.

2 Unsworth DJ, Leonard JN, McMinn RMH, Swain AF, Holborow EJ, Fry L. Antigliadin antibodies and small intestinal mucosal damage in dermatitis herpetiformis. *Br J Dermatol* 1981; **105**: 653-8.

3 Unsworth DJ, Kieffer M, Holborow EJ, Coombs RRA, Walker-Smith JA. IgA antigliadin antibodies in coeliac disease. *Clin Exp Immunol* 1981; **46**: 286-93.

4 McMillan SA, Haire M. Smooth muscle antibody in patients with warts. *Clin Exp Immunol* 1975; **21**: 269-74.

5 Rizzetto M, Doniach D. Types of reticulin antibody detected in human sera by immunofluorescence. *J Clin Pathol* 1973; **26**: 841-51.

6 Unsworth DJ, Manuel PD, Walker-Smith JA, Campbell CA, Johnson GD, Holborow EJ. A new immunofluorescent blood test for gluten sensitivity. *Arch Dis Child* 1981; **56**: 864-8.

7 Seah PP, Fry L. Immunoglobulins in the skin in dermatitis herpetiformis and their relevance in diagnosis. *Br J Dermatol* 1975; **92**: 157-66.

8 Stern M, Fischer K, Gruttner R. Immunofluorescent serum gliadin antibodies in children with coeliac disease and various malabsorptive disorders. *Eur J Pediatr* 1979; **130**: 155-64.