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DERMATITIS HERPETIFORMIS: RELATION BETWEEN CIRCULATING ANTIBODIES AGAINST RETICULIN AND GLUTEN, SMALL-INTESTINAL MUCOSAL STATUS AND ABSORPTIVE CAPACITY

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Abstract. The status of the jejunal mucosa and of the intestinal absorptive capacity were investigated and related to the occurrence of antibodies against reticulin and gluten in 55 patients with dermatitis herpetiformis (DH), 28 on a normal, 11 on a gluten-reduced and 16 on a gluten-free diet. The mucosal status was characterized on the basis of histopathological findings and the numbers of intra-epithelial lymphocytes. Absorption was evaluated by 5-h urine and 1-h serum D-xylose tests. There was a positive correlation between the degree of pathological mucosal changes, malabsorption and the occurrence of circulating antibodies against reticulin and gluten. The serum xylose test was more sensitive than the urine xylose test for screening of the relatively mild enteropathy of DH and identified 88% of the patients with an abnormal mucosal status. The serological test (antibodies to reticulin and gluten) identified 80% of such patients. Among patients on a gluten-free diet there was some discrepancy between the serum xylose and the serological test, in that 5 of the 16 patients on this diet had an abnormal serum xylose test result, but no antibodies. In DH patients on a normal diet, the presence of antibodies to reticulin and gluten provided the same information about the presence of mucosal lesions as the serum xylose test. In the whole material a combination of the serum xylose test and the serological test identified 24 of 25 patients with an abnormal mucosal status.

Key words: Dermatitis herpetiformis; Gluten antibodies; Reticulin autoantibodies; D-Xylose tests; Intra-epithelial lymphocytes

Patients with dermatitis herpetiformis (DH) frequently have a gluten-induced enteropathy indistinguishable from that in coeliac disease (14). Elimination of gluten from the diet in DH improves the intestinal lesion to the same extent as in coeliac disease (14) and there is now also general agreement that in most DH patients the skin lesions respond to gluten withdrawal (9).

In an earlier prospective study we investigated the occurrence of circulating antibodies to reticulin and gluten in DH patients and found that the incidences of both antibodies were reduced by withdrawal of gluten from the diet (12).

The present study was carried out to analyse the relationship between the occurrence of antibodies against reticulin and gluten, on the one hand, and the small-intestinal mucosal status, based on histopathological findings and D-xylose tests, on the other.

Severe malabsorption as occurs in coeliac disease has been reported to be infrequent in DH (14), an observation which in recent years has drawn attention to a need for more sensitive screening tests for the milder forms of gluten-sensitive enteropathy (6).

The serum xylose test is claimed to be more sensitive than the urine xylose test for identification of malabsorption (7). However, its significance compared with the urine xylose test is still under debate. An additional aim of the study was therefore to compare these two tests with each other and also with a serological test determining gluten and reticulin antibodies, with respect to their efficiency in identifying the often rather discrete small-intestinal dysfunction in the DH patients.

MATERIAL AND METHODS

Patients

Fifty-five patients with dermatitis herpetiformis (DH) were investigated (Table I). All had typical pruritic, papulovesicular skin lesions and in all cases the histopathological findings were in agreement with the diagnosis. Moreover, all patients responded promptly to dapsone therapy. Granular IgA deposits in the papillary dermis were found in all of them. After interviews concerning dietary habits and bowel symptoms, skin biopsies and blood samples were taken and the patients were informed about a gluten-free diet and its potential beneficial effects in DH. Sixteen subjects chose this diet, and 14 of them were followed for more than 2 years while undergoing this

Table I. *Patient material*

Diet groups	Number of patients		Mean age (yrs) at follow-up ± SD (range)	Duration of follow-up (months) (range)	Mean duration of DH (yrs) at follow-up ± SD (range)
	Female	Male			
Gluten-free ($n=16$)	5	11	46±15 (24–71)	32±11 (6–42)	16±10 (1–36)
Gluten-reduced ($n=11$)	2	9	47±14 (28–71)	19±8 (7–29)	11±5 (3–17)
Normal ($n=28$)	11	17	60±14 (35–81)	17±7 (17–47)	18±12 (4–56)

treatment. Eleven patients chose to take a gluten-free diet in their own homes but had ordinary food elsewhere. Their diet is referred to as "gluten-reduced". The remaining patients continued on a normal gluten-containing diet (data for the patients are given in Table I).

The dapsone requirement decreased in all patients on a gluten-free diet and 6 of these patients had even discontinued this medication at the time of follow-up investigation. Most patients on the gluten-reduced diet were also able to lower their dapsone consumption, while in the normal diet group no consistent dapsone reduction were possible. Details about the dapsone requirement on the different diets will be given elsewhere (13).

All patients had normal serum creatinine values and none of them were taking drugs known to affect absorption or renal clearance of xylose.

METHODS

Serum folate was determined at the start of the dietary period and at follow-up by means of a standard analytical technique as part of the diagnostic routine at the Department of Clinical Chemistry. A value of 7–34 nmol/l was considered normal.

D-Xylose absorption test. 25 g of D-xylose dissolved in 500 ml of water was administered orally to the patients in the morning after an overnight fast. Urine was collected for the following 5 hours and serum samples were drawn one hour after the administration. Xylose concentrations in urine and serum were determined as described by Rozental & Tomaszewski (15). Based on a local control material, a concentration in the serum after one hour of more than 2.3 mmol/l and an excretion in the urine of more than 18.1 % of the given dose were considered normal.

Serological test

Determinations of circulating antibodies against gluten were made with sections of wheat grain and gliadin-coated Sepharose beads as antigens (8, 12). Reticulin autoantibodies in the serum were investigated as described earlier (11). Details concerning the effects of the diets on the occurrence of both these antibodies will be given elsewhere (12).

Small-intestinal biopsy

One or two biopsy specimens of the jejunal mucosa were obtained just distal to the duodeno-jejunal junction by the Crosby technique for small-intestinal biopsy. The specimens were fixed in neutral buffered 10% formalin for 24 hours. During the paraffin wax embedding the specimens were properly oriented with the mucosal surface perpendicular to the cutting surface. Sections 5 μm thick were stained with haematoxylin-eosin. The villous atrophy was classified as "subtotal" (no or almost no villi, elongated crypts and extensive inflammatory reaction of the chronic type in the lamina propria) or "partial" (broad, often shortened villi, with slight crypt hyperplasia and slight or moderate inflammation). In each specimen the total number of intra-epithelial lymphocytes (IEL) per at least 500 epithelial cell nuclei was counted according to the method of Ferguson and Murray (3). This quantitation of lymphocytes was performed only on villi or mucosal surface (in subtotal atrophy). A lymphocyte count below 40/100 epithelial cells was considered normal (3). The histological examination and the counting of IEL were carried out without knowledge of the patient's diet group.

Intestinal biopsies and xylose absorption tests were only performed at the follow-up examination.

Not all patients were studied with all methods and some specimens and samples were lost, and therefore the number of patients in the figures and tables is smaller than the total patient population. Histopathological examination of the jejunal mucosa was carried out in 51 patients, quantification of IEL in 45, both urine and serum xylose

Table II. *Mean values and standard deviations for the 1-hour serum concentrations (mmol/l) and 5-hour urine excretion of D-xylose (% of given dose) in the three diet groups*

	Serum xylose	Urine xylose
Normal diet ($n=24$)	1.63±0.67[a]	18.0±7.0[c]
Gluten-reduced diet ($n=10$)	1.85±0.72[b]	26.1±6.6
Gluten-free diet ($n=16$)	2.54±0.76	24.4±6.6

[a] $p<0.001$ compared with gluten-free diet (t-test).
[b] $p<0.05$ compared with gluten-free diet (t-test).
[c] $p<0.01$ compared with gluten-free and gluten-reduced diets (t-test).

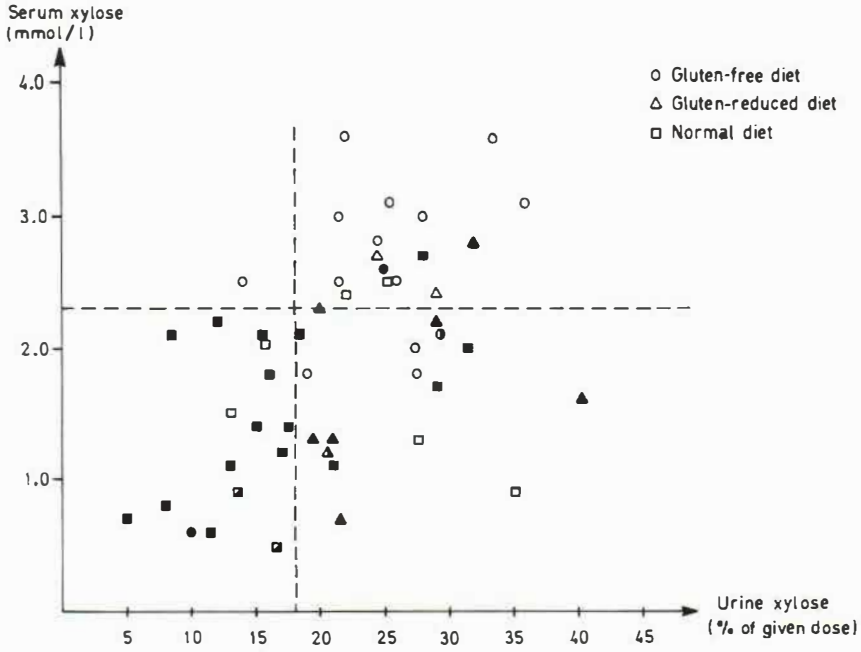

Fig. 1. One-hour serum xylose concentration after a 25 g xylose load and 5-h urinary xylose excretion in relation to diet in patients with dermatitis herpetiformis. Solid symbols denote an abnormal mucosal status (villous atrophy and/or more than 40 intra-epithelial lymphocytes/100 epithelial cells). Half-filled symbols denote that both or either of the methods of examination of the intestinal mucosa were not used. The interrupted lines represent the lower limit of the normal ranges.

tests in 50 and estimation of both gluten and reticulin antibodies in 54.

Patients receiving folate therapy during the study period were excluded from the calculation of mean values.

RESULTS

Symptoms

When this study began, 22 patients (41%) had daily intestinal symptoms such as diarrhoea, distension and pain. Fourteen (26%) had diarrhoea regularly and at times 3 of them were unable to work for this reason. Some additional patients, when specially questioned, admitted bowel symptoms, but these were, however, difficult to evaluate and are therefore not included. Eight of the patients with gastro-intestinal symptoms followed the gluten-free diet regimen. Four had a gluten-reduced diet and the remaining 10 continued on a normal diet. There was a self-selection for patients with the most serious bowel problems to the gluten-free and gluten-reduced diet groups. At follow-up none of the patients on a gluten-free diet had gastro-intestinal symptoms. All of them had already become totally relieved of such symptoms some months after starting on the diet. They had noted deterioration when sometimes failing to observe the diet strictly. Two of the patients on a gluten-reduced diet and 9 of those on a normal diet still had gastro-intestinal symptoms at follow-up.

At the commencement of the study there were no significant differences in mean serum folate concentrations between the groups of patients who were to start on a gluten-free, gluten-reduced and normal diet (16.3 ± 10.0 (SD), 10.3 ± 5.0 and 11.4 ± 4.0 nmol/l respectively). At follow-up these values had increased significantly in the gluten-free and gluten-reduced diet groups (25.2 ± 14.5; $p<0.01$ compared with value at start and with the value for the normal diet group, t-test; and 14.0 ± 6.1; $p<0.02$ compared with value at start, t-test; respectively). On a normal diet the mean value remained unchanged, and at follow-up 7 patients on this diet had low values or had received substitution therapy because of deficiency, as compared with none on the other diets.

D-Xylose tests

The mean values for both serum and urine xylose at

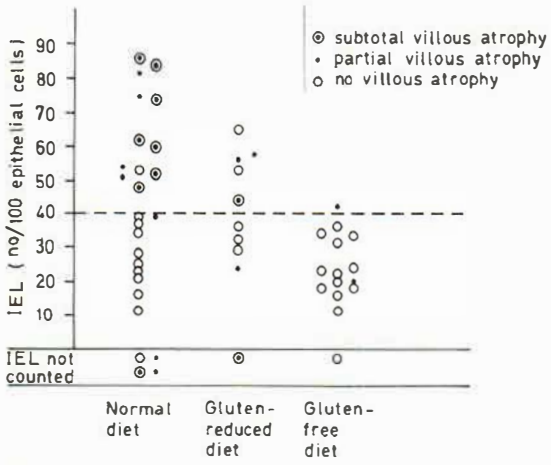

Fig. 2. Number of intra-epithelial lymphocytes (IEL) in relation to intestinal mucosal changes in patients with dermatitis herpetiformis grouped according to diet. The interrupted line denotes the upper limit of the normal range. The mean IEL count in the patients on a gluten-free diet was significantly lower ($p<0.01$; t-test) than in those on a gluten-reduced or a normal diet 25±9 (SD), 44±15 (SD) and 48±23 (SD) lymphocytes/100 epithelial cells respectively.

follow-up were higher in the group on a gluten-free than in those on a normal diet (Table II).

In 50 patients the 1-hour serum value and the 5-hour urine excretion of xylose were determined simultaneously. In 33 patients the result of the serum xylose test was abnormal and in 17 the urine xylose excretion was decreased. Sixteen of the 33 patients with a low 1-hour serum xylose concentration also had an abnormal urine xylose test, while all patients but one with a reduced urine excretion of D-xylose also had a low serum value (Fig. 1).

Fifteen of the 24 patients on a normal diet had abnormal results of both the serum and urine xylose tests, while 3 patients had normal values for both tests. Five of the 16 patients on a gluten-free diet had abnormal serum xylose tests and in one of these patients the values for both xylose tests were too low (Fig. 1). These differences were statistically significant ($p<0.001$; χ^2 test).

Mucosal status

Subtotal or partial villous atrophy was found in 15 of 26 patients on a normal diet, in 5 of 10 on a gluten-reduced diet and in 2 of 15 on a gluten-free diet (Fig. 2). When increased IEL counts were also taken into consideration, evidence of mucosal lesions was found in one further patient on a normal diet and in 2 further patients on a gluten-reduced diet. Significantly more patients on a normal diet than on a gluten-free diet had an abnormal mucosal status ($p<0.01$; χ^2 test).

There was good agreement between villous atrophic changes and IEL counts (Fig. 2). Of 18 jejunal specimens with atrophy, 15 had IEL counts exceeding the upper normal limit and all biopsy specimens with subtotal villous atrophy had increased IEL counts. In 3 partially atrophic specimens the IEL counts were in the normal range, whereas, among 27 morphologically normal biopsies 3 had raised IEL values (Fig. 2). All patients with gastro-intestinal symptoms and all with folate deficiency, in whom the mucosal morphology was evaluated and IEL counts performed, showed evidence of mucosal lesions. However, only 5 of the 10 patients with subtotal villous atrophy had bowel symptoms.

Relationship between mucosal status and xylose tests

Fig. 1 illustrates the relationship between the status of the small-intestinal mucosa and the xylose tests. Of 25 patients with an abnormal mucosal status, 22 had an abnormal serum xylose test and 12 an abnormal urine xylose test. In 12 of 14 patients with simultaneously abnormal serum and urine xylose tests an abnormal mucosal status was found. This group contained all subjects with folate deficiency and 6 out of 10 with subtotal villous atrophy. Of 29 patients with an abnormal serum xylose test, 7 had a normal mucosa. All patients with subtotal villous atrophy had a low serum xylose value.

Of the 17 patients showing normal value in the serum xylose test, 3 had partial villous atrophy.

The mean IEL count/100 epithelial cells in the patients with abnormal results in both xylose tests was 56±17 (SD), in those in whom only the serum xylose test was abnormal, 45±22; and in whom neither test was abnormal, 28±15. The difference in IEL values was significant between all three groups ($p<0.05$–<0.001; t-test).

Relation between mucosal status and antibodies against reticulin and gluten

At follow-up 20 of 25 patients with an abnormal mucosal status had antibodies to reticulin and/or gluten (Fig. 3). Among the 10 patients with subtotal villous atrophy (all with intake of gluten) 9 had one

or both antibodies; gluten antibodies were present in 7 and reticulin autoantibodies in 4. Twelve patients with gluten consumption (normal and gluten-reduced diet) had a normal mucosa. In these subjects altogether 6 patients had either antibody or both; gluten antibodies were present in 5 and reticulin autoantibodies in 2. (In one of these 12 patients reticulin autoantibodies were not determined.)

Of 26 patients with one or both antibodies, 11 had antibodies to reticulin and 25 to gluten. Twenty (77%) of these 26 individuals had an abnormal jejunal mucosa (9 with subtotal and 11 with partial villous atrophy), while only 5 (24%) of the 21 patients without antibodies had a mucosal lesion (1 with subtotal and 4 with partial atrophy) ($p<0.01$; χ^2-test).

An abnormal mucosal status was found in 8/11 patients with only IgG class gluten antibodies and in 9/12 with gluten antibodies of the IgA class alone or together with those of the IgG class.

Since in most patients with reticulin autoantibodies these were of both the IgA and IgG class, the correlation between each class separately and mucosal damage was not examined.

A relation was found between the titres of reticulin autoantibodies and the degree of villous atrophy in that patients with the highest titres (1/100) had subtotal villous atrophy and those with a low titre (1/10) had a normal or partially atrophic mucosa.

Relation between xylose test and serological test

Most patients (73%) with an abnormally low serum xylose value had a positive serological test (antibodies against gluten and/or reticulin) (Fig. 4). Of patients with a normal serum xylose test, 29% had one of these antibodies in their sera.

There was agreement between the serum xylose and the serological tests in 35 of 50 cases. Among 15 cases without agreement the serological test was positive in 5 (3 with normal and 2 with an abnormal mucosal status) and the xylose test in 10 (4 each with a normal and an abnormal mucosal status and 2 not biopsied). Of these 15 subjects without test agreement, 11 patients were on a gluten-reduced or gluten-free diet. Among 24 patients on a normal diet there was complete agreement between the tests in 20. Of the remaining 4 without agreement, 2 (1 each with a normal and an abnormal mucosal status) had a low serum xylose value and 2 (both with normal mucosa) had antibodies in their sera. Among the 16 patients on a gluten-free diet there was agreement between the tests in 10, and among the 6 without agreement, 5 (3 with a normal and 1 with an abnormal mucosal status and 1 not biopsied) had a too low serum xylose value and only 1 (with abnormal mucosa) had antibodies in the serum.

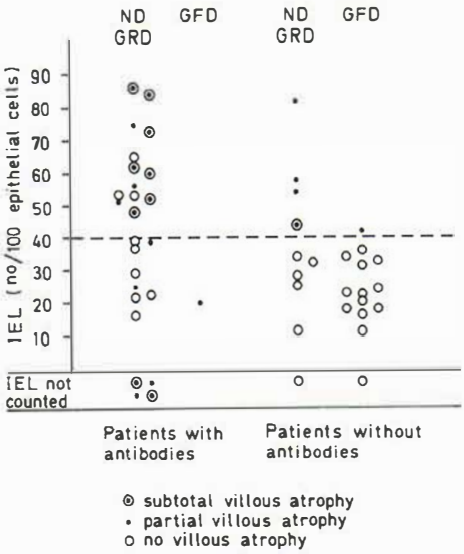

Fig. 3. Number of intra-epithelial lymphocytes (IEL) in relation to intestinal mucosal changes in patients with dermatitis herpetiformis grouped according to the presence of circulating antibodies to gluten and/or reticulin. The interrupted line denotes the upper limit of the normal range. ND = normal diet; GRD = gluten-reduced diet; GFD = gluten-free diet.

DISCUSSION

In this study of 55 patients with DH, an interrelationship was found between an abnormal jejunal mucosal status, malabsorption and circulating antibodies against reticulin and gluten, and these factors were found to be dependent on a gluten-containing diet. A beneficial effect of gluten withdrawal from the diet on the dermatitis in these cases was demonstrated in a previous investigation (13). These findings, all obtained on one and the same material, are in agreement with a number of previous reports where usually fewer parameters at one time (4, 7, 10, 17, 19) have been shown to be correlated. In the present material the findings in patients on a gluten-free diet were significantly more normal than in those who had consumed gluten, both serologically and with respect to the mucosal morphology and

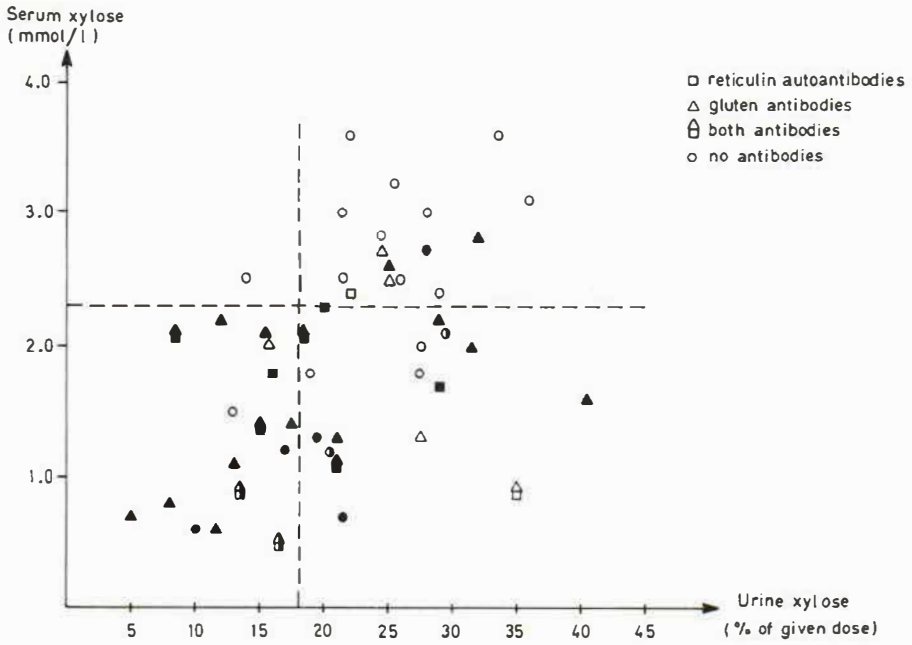

Fig. 4. One-hour serum xylose concentration after a 25 g xylose load and 5-h urinary xylose excretion in patients with dermatitis herpetiformis in relation to the presence of circulating antibodies to gluten and reticulin. Solid symbols denote (as in Fig. 1) intestinal mucosal damage, while half-filled symbols denote that both or either of the methods of examination of the intestinal mucosa were not used. The interrupted lines represent the lower limit of the normal ranges.

function. The effect of the diet on the intestine could not be evaluated exactly in this study, however, as the biopsies and xylose loading tests were performed only at its conclusion. However, a significant increase in serum folate values and complete disappearance of bowel symptoms in the gluten-free diet group, which consisted of patients with the most pronounced symptoms at the start, indicate that the gluten-free diet had a curative effect on the intestine. Moreover, 2 patients on this diet with subtotal villous atrophy at the start showed a normal mucosa in the follow-up biopsy. The intestinal restitution coincided with the ability of the patients on this diet to reduce their initial dapsone requirement significantly (13). It should be pointed out that severe mucosal lesions and evidence of malabsorption were found also in patients without symptoms (5, 6). On the other hand, intestinal symptoms or folate deficiency invariably indicated an abnormal mucosal status.

The patients on a gluten-reduced diet had just as severe intestinal lesions as those on a normal diet, but their need for dapsone was reduced by the diet restriction to half their initial dose (13). Frödin et al. (5) noted some improvement of the mucosal changes in patients on this type of diet.

The urine D-xylose test failed to indicate half of the abnormal mucosae and is apparently not useful as a screening test for mucosal damage in DH, an experience also reported by Gillberg et al. (6).

The serum xylose test was more sensitive for the identification of jejunal mucosal damage. Moreover, the 1-hour serum xylose test is not influenced by the renal function or by incomplete urine collection, which might falsely indicate intestinal malabsorption in the urine xylose test (7). Consequently, the 1-hour serum xylose test is recommended rather than the 5-hour urine xylose test as a method of screening for jejunal enteropathy in DH.

This study like others (16) shows that except when present in a very low titre, reticulin autoantibodies indicate enteropathy in DH and are therefore of value as a diagnostic aid. However, they cannot be used unconditionally in screening for intestinal damage as their incidence in this condition is relatively low. Eade et al. (2) reported that reticulin autoantibodies of the type 1 pattern and of the IgA class are the only antibodies against reticulin

significantly associated with coeliac disease. In our study the reticulin autoantibodies were exclusively of type 1 (12) and in most cases of both IgA and IgG classes.

Serum analysis of antibodies against gluten has been shown to be of value in the diagnosis of gluten-sensitive enteropathy and as a follow-up test during treatment with a gluten-free diet (17). Gliadin antibodies of the IgA class have been claimed (18) to be more specific for gluten-sensitive enteropathy in children than those of the IgG class, which have also been found in other types of mucosal damage and even in patients with a normal mucosa.

Our study did not permit any conclusions to be drawn regarding the significance of each antibody class in differentiating patients with mucosal damage of different aetiologies. As an indicator of mucosal damage in DH, however, gluten antibodies of IgG class seemed to be at least as efficient as those of the IgA class.

Several authors have claimed that the persistence of antibodies to gluten indicates continuing gluten intake (1, 17). Only one of our patients on a gluten-free diet had gluten antibodies at the final examination, which supports such a concept, especially as this patient had partial villous atrophy and also had only managed to reduce her dapsone dose slightly in comparison with others on this diet.

An abnormal serum xylose test result was recorded in 5 patients on a gluten-free diet, although they did not have antibodies to gluten or reticulin. If this test reliably reflects the absorptive capacity of the small intestine (7), these observations suggest either that continued gluten intake in these patients will not stimulate antibody production, as discussed earlier for reticulin antibodies (10), or that factors other than gluten might be of importance for malabsorption in some patients. A patchy distribution of villous atrophy occurs to some extent both in DH and in coeliac disease (14). Since, like many other investigators, we were not able to take more than one or two biopsies from each patient, mucosal areas with some villous atrophy might have been missed. Moreover, minor intestinal lesions which are too discrete to be classified as abnormal with the presently used histopathological criteria might cause a disturbed absorption. If the upper limit for a normal IEL count had been lowered to 30 lymphocytes/100 epithelial cells, as proposed by Fry (4), 2 of the 3 patients on a gluten-free diet with an abnormal serum xylose value, who are now considered to have a normal mucosa, would instead have been classified as having an abnormal one.

In the patients on a normal diet there was fairly close agreement between the serum xylose and the serological tests. Thus, in patients on this diet, simultaneous determination of antibodies to gluten and reticulin might be as good a screening test for mucosal damage as the serum xylose test.

In conclusion, both the serum xylose test and the serological test were better for screening of an abnormal mucosal status in DH than the usually employed urine xylose test, and when they were combined almost all patients with an abnormal mucosa were identified.

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