

GASTROINTESTINAL INVESTIGATIONS IN DERMATITIS HERPETIFORMIS

O. Fausa, T. Eeg Larsen, G. Husby and P. Thune

From the Departments of Dermatology, Medicine A, Pathology, and the Institute of Immunology and Rheumatology, Rikshospitalet, Oslo, Norway

Abstract. Thirty-seven patients with dermatitis herpetiformis (DH) have been investigated for gastric and small intestinal abnormalities. Evidence of an enteropathy was found in 86% of the patients who had IgA deposits in uninvolved skin. Villous atrophy of the small intestine was found in 29 patients. About one-half of the patients had reduced absorption of xylose and vitamin A. The Schilling test value was lowered in one-third. Serum B₁₂ was too low in 5/28 patients whereas folic acid in serum and whole blood was too low in 14/29 and 5/19, respectively. Atrophic gastritis occurred in 14/28 patients and only about one-third of the whole patient material had normal gastric mucosal structure and secretion.

Key words: Dermatitis herpetiformis; Gastric acidity; Hypochlorhydria; Malabsorption

At the present time the best diagnostic criteria for dermatitis herpetiformis (DH) appear to be findings of IgA deposits in the uninvolved skin and evidence of an enteropathy (8). However, the clinical symptoms of malabsorption are mostly slight and easily overlooked in DH as compared with coeliac disease (CD), although mucosal abnormalities are almost invariably demonstrated if a sufficient number of biopsies are taken (4).

Several recent investigations indicate that the enteropathy in DH is identical with that of CD and improves on a gluten-free diet (10, 15, 21, 22). It is also reported that the skin lesions in DH are gluten-dependent and may clear if a strict diet is maintained for longer periods, of months or even years (9, 14).

Reduced secretion of gastric acid has been reported in DH as well as in CD (1). In the present work we have investigated more closely the frequency and severity of the gastric and small intestinal abnormalities in DH.

MATERIAL AND METHODS

Thirty-seven patients (aged 18-77 years) including 23 males and 14 females, were studied. Nineteen patients were 50

years or younger. The duration of symptoms varied from $\frac{1}{2}$ to 40 years (mean 10 years). All patients were hospitalized during the study and all were treated with Dapsone® or sulphapyridine prior to or during the examinations. None of them was on gluten-free diet.

The patients were diagnosed according to the following criteria: clinical features, response to iodine provocation orally (1 or possibly 2 g KJ mixture), histology of skin lesions, immunofluorescence studies of uninvolved skin, and response of skin lesions to sulphone therapy. The demonstration of IgA in uninvolved skin by direct immunofluorescence microscopy was considered to be most important in establishing the correct diagnosis (5, 8), and was performed as follows: Frozen sections (4 μ m) from skin biopsies were stained with fluorescein isothiocyanate (FITC)-conjugated antisera to human IgA, IgG IgM and C₃ as described previously (12, 13). The stained sections were examined in a Leitz Orthoplan microscope equipped with UV light source and filter combination for FITC (13).

In addition to several general blood tests (erythrocyte sedimentation rate, haemoglobin, white blood cell count, serum iron, total iron binding capacity, SGOT, SGPT, blood urea nitrogen, serum protein electrophoresis) the following gastroenterological investigations were carried out:

Pentagastrin test. Gastric acid secretion after Pentagastrin stimulation (6 μ g/kg body weight subcutaneously); below 11 mEq/h (MAO) was considered to be abnormal. Achlorhydria: MAO < 1 mEq/h and pH > 3.5.

Secretin test. This was performed as described by Petersen (18).

D-xylose absorption. An oral test dose of 25 g was given to fasting patients. Urinary excretion of less than 4.0 g was considered as pathological.

Vitamin A absorption. Plasma values of more than 800 i.u. at 4 hours after an oral load of 350 000 i.u. was considered as normal.

Schilling test for vitamin B₁₂ absorption. Normally 10% or more of the radioactive vitamin B₁₂ is excreted in 24 hours.

Folic acid in serum and whole blood. Normal values > 3 ng/ml and > 30 ng/ml, respectively.

Vitamin B₁₂ in blood. Normally > 160 pg/ml.

Jejunal and gastric biopsies

Suction biopsies were obtained using a multiple biopsy capsula, the position being controlled fluoroscopically. Dissecting microscopy and histological examinations were performed (11, 21).

RESULTS

On admission to hospital the following abnormalities in 16/21 subjects could be related to a malabsorption state: diarrhoea (5), megaloblastic anaemia (7) excessive weight loss (3), oedema (1). In addition 4 patients complained of dyspepsia. The other patients had no gastrointestinal symptoms, or precise information was not obtained. There was no correlation between the gastric and small intestinal changes, the duration or intensity of the skin disease, and the age of the patients.

Granular deposits of IgA were demonstrated in the dermo-epidermal junction of uninvolved skin in 23 patients (Fig. 1). Of 3 patients who had symptoms of both CD and DH, IgA was demonstrated in one, both IgA and IgM in the second, and in the third no immunoglobulins could be detected. The specificity of the immunofluorescence was checked previously (12, 13).

No immunofluorescence microscopy was performed in the remaining 11 patients but they fulfilled all the other criteria for the diagnosis of DH.

Histological studies of the biopsies from the small intestine showed lesions with marked villous atrophy in 17/37 patients (46%) and 12/37, i.e. about one-third, had more moderate villous changes. A normal intestinal mucosa was found in 8/37 patients. In total, 19 out of the 23 patients with IgA deposits in the skin had total or partial villous atrophy.

Table I shows the results of the different function tests. About one-half of the patients had reduced

Table I. Results of intestinal function tests performed in patients with dermatitis herpetiformis

	Number of patients		
	Totally tested	Normal values ^a	Low values
Vitamin A absorption	28	14	14
Xylose absorption	23	12	11
Vitamin B ₁₂ absorption	21	14	7
Vitamin B ₁₂ in blood	28	23	5
Folic acid			
(a) Serum	29	15	14
(b) Whole blood	19	14	5

^a Normal values: Schilling test $\geq 10\%$ of the radioactive B₁₂ dose excreted in 24 hours. Vitamin B₁₂ > 160 pg/ml. Serum folic acid > 3 ng/ml and whole blood folate > 30 ng/ml.

absorption of xylose and vitamin A. The Schilling test of vitamin B₁₂ absorption was reduced in one-third of the patients. Serum vitamin B₁₂ was too low in 5/28 patients, whereas folic acid in serum and whole blood was too low in 14/29 and 5/19 patients, respectively.

Table II shows the results of the gastric secretory studies and biopsies. In 14/28 patients the histologic features were characteristic of atrophic gastritis. Twelve of these patients had hypo- or achlorhydria. Furthermore, hypo- or achlorhydria was detected in 5/8 patients with non-atrophic gastritis. Of 6 patients with a normal gastric biopsy, one showed hypochlorhydria. Nine patients had no biopsy

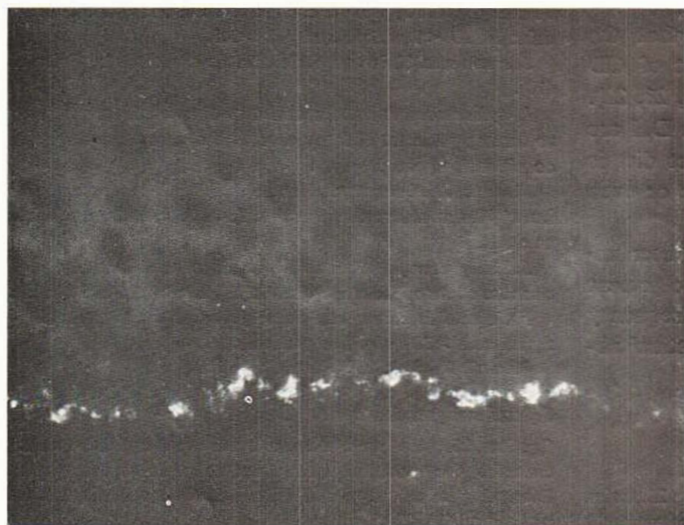


Fig. 1. Immunofluorescence micrograph. Frozen section of skin biopsy from a patient with dermatitis herpetiformis, stained for IgA, showing granular deposits of IgA in the dermo-epidermal junction ($\times 260$).

Table II. *Histologic appearance and gastric acid secretion in patients with dermatitis herpetiformis*

	Gastric acid secretion				
	Total	A-chlor- hy-dria	Hypo- chlor- hy-dria	Normal	Not examined
Atrophic gastritis	14	9	3	1	1
Chronic gastritis	3	0	2	1	
Gastritis ^a	5	3		1	1
Normal	6		1	5	
No biopsy	9	2	1	3	3

^a Biopsy not representative.

but hypo- or achlorhydria was detected in 3. In total, hypo- or achlorhydria was detected in 21 patients. The secretin test showed normal values in all patients tested.

DISCUSSION

The present study confirms previous findings of gastric and small bowel changes in DH patients. With strict diagnostic criteria, in particular the demonstration of IgA in uninvolved skin, the frequency of gastrointestinal abnormalities increased.

Only about one-third of our total patient material had normal gastric mucosal structure and secretion. Andersson et al. (1) observed achlorhydria in 3 and low gastric secretion in 6 out of 10 patients with DH. Hansky & Shiner (11) found achlorhydria in 4/15 patients with coeliac disease while 6/15 had varying degrees of mucosal atrophy. A high frequency of atrophic gastritis and achlorhydria in adult coeliac disease is also described by Cooke (6).

In comparison, gastric biopsies and acid secretion measurements performed in our laboratory in 32 patients with CD (7) gave the following results: 22 had a normal gastric mucosa histologically, 7 patients had reduced acid secretion and only 2 of these had achlorhydria. This indicates that DH patients may have a higher incidence of gastric abnormalities than patients with CD. The possibility exists that a high incidence of atrophic gastritis might be associated with advancing age rather than with the patient's primary disease. In our materials with DH and CD patients the gastric changes seemed to be unrelated to the age of the patients. The

fact that normal acid secretion may be found in patients with atrophic gastric mucosa and, conversely achlorhydria in patients with a normal biopsy, is presumably due to the patchiness of the lesions.

At least two of the malabsorption tests performed revealed signs of enteropathy in 50% of the patients with DH. About one-third presented overt symptoms clinically. It is assumed that in those patients who do not absorb B₁₂, the entire intestine is abnormal and will present a flat mucosa (6). It could be expected that an atrophic gastritis may contribute to this malabsorption. The reduction of intrinsic factor secretion, however, does not usually fall within the range of pernicious anemia (1) and, in the cases tested by us, intrinsic factor gave no improvement in B₁₂ absorption. In this study all patients were treated with sulphones. Presumably this therapy affects only the skin lesions and does not influence the gastrointestinal abnormalities.

Biopsy of the small intestine presented evidence of an enteropathy in 86% of the patients who had IgA deposits in uninvolved skin. This incidence is a little less than in the recent data reported by Fry & Seah (8). One reason for this may be that we did not perform intestinal lymphocyte counts. Clearly, all DH patients do in fact have intestinal abnormalities but they are more difficult to demonstrate than in CD, as the mucosal lesions are more patchy.

The following features are common in both DH and CD: the intestinal abnormalities improve as one proceeds from proximal to distal small intestine (4), the enzymatic disaccharidase and dipeptidase activities diminish (3), and improvement occurs on gluten-free diet (9, 14). Several findings indicate an immunological mechanism: antireticulin antibody occurs in DH and CD, the titre falls slowly on gluten-free diet (20), cross reactivity has been demonstrated between fraction III of gluten and reticulin (19). Circulating immune complexes are present in the sera of most patients with gluten-sensitive enteropathy (17) and the immunoglobulin findings in the intestinal mucosa seem to be identical in DH and CD (2). In addition, similar HL-A antigens occur in the two diseases (23).

It has been suggested that there is a reticulin defect in the small intestine in both DH and CD and that in the former the defect is also found in the skin (19).

Another hypothesis is offered by van der Meer (16). In his view the IgA deposits in the skin originate

in the gut and are transported as soluble substances in the blood circulation. Thus the primary site of pathological events may be in the gut, i.e. the lymphoid tissue, with production of IgA by plasma cells in the intestinal mucosa.

The discrepancy in symptoms between DH and CD is explained by the patchy distribution of mucosal lesions in the former (4). The reason for this difference, however, is not clear. Since it has been shown that the skin lesions and not only the enteropathy in DH are related to gluten sensitivity (9, 14) it therefore seems justified to treat these patients not only with sulphones but also with a gluten-free diet. In addition one should not forget that the enteropathy might be connected with an increased incidence of malignancy just as in CD (6). With these facts in mind, it is essential that every patient who is suffering from DH should have full gastrointestinal investigations and a diagnosis established according to strict criteria.

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P. Thune, M.D.
Department of Dermatology
Rikshospitalet
Oslo
Norway