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GASTROINTESTINAL DYSFUNCTION IN DERMATITIS HERPETIFORMIS

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Abstract. Nine patients with dermatitis herpetiformis were investigated for intestinal dysfunction. In six patients small intestinal mucosa showed "disappearance" of villi. The disaccharidase activities of the mucosa were abnormal in five of eight patients studied and the dipeptidase activities in six.

Dermatitis herpetiformis is often associated with disturbed function of the small bowel (9, 10, 16, 17, 23, 25). Severe histopathological changes of the small intestine with disappearance of the villi have also been described (2, 9, 10, 16, 17, 23, 25). The stereomicroscopical and histological appearance of the jejunal mucosa in the enteropathy of dermatitis herpetiformis is similar to that of the coeliac syndrome, but the malabsorption is less pronounced (23).

In untreated coeliac disease the disaccharidase activity (1, 6) as well as the dipeptidase activity (15) of the small intestine is decreased. Remission of the disease, usually in response to gluten-free diet, results in an increase of the enzyme activities in the mucosa (15, 20). Fraser et al. (9) also found disaccharidase activity (maltase, lactase and sucrase) to be related to the histologic appearance of the small intestine in dermatitis herpetiformis. No investigations of the dipeptidases of the intestinal mucosa in dermatitis herpetiformis have been published.

In the present investigation of patients with dermatitis herpetiformis, routine gastrointestinal studies were performed as well as measurements of disaccharidase activity and dipeptidase activity in small-intestinal mucosal biopsies.

CLINICAL MATERIAL AND METHODS

Nine patients, 8 men and 1 woman, age 25 to 73 years, were examined. They had had dermatitis herpetiformis for 8 to 28 years. All of them had been treated with diaminodiphenylsulfone (Avlosulfon, ICI) for 3 to 11 years and were receiving such treatment at the time of the investigation. The sulfone dose varied between 0.05 and 0.4 g and was usually 0.1 g daily. Doses of more than 0.2 g had been taken against doctors' advice when the symptoms were very severe. All nine patients were hospitalized during the investigation. They had been admitted either because the skin symptoms were difficult to control or because anemia had developed during treatment. The patients were specifically questioned regarding previous or recent gastrointestinal symptoms and in all of them radiological examination of the gastrointestinal tract by barium contrast was performed.

Hemoglobin, red blood cells, reticulocytes, serum iron, total iron binding capacity, serum haptoglobin and sternal marrow were examined by conventional methods.

The serum B_{12} content was measured by an isotope technique (24). Values between 150 and 900 pg/ml were regarded as normal.

Folic acid in whole blood and in the serum was assessed with *Lactobacillus casei* at the Central Chemical Laboratory, Sahlgren's Hospital, Gothenburg (12). Serum values between 2.8 and 3.5 ng/ml and whole blood values between 40 and 150 ng/ml were regarded as normal.

Formiminoglutaminic acid (FIGLU) in the urine was estimated after loading with 15 g of histidine per os. Excretion of more than 20 μM/hour was regarded as abnormal.

Vitamin B_{12} absorption was studied with the Schilling test, values above 10% being regarded as normal.

D-xylose absorption was measured by analysis of the amount excreted in the urine within 5 hours after an oral dose of 5 g D-xylose. Less than 1.4 g was regarded as abnormal.

Faecal fat excretion was determined as the average per day after collection for 3 days with the patient on a normal ward diet (14). More than 5 g fat per day was considered abnormal.

Peroral mucosal biopsy of the small intestine was performed with a Crosby capsule at the duodeno-jejunal flexure under fluoroscopic control. In one patient (no. 1), operated upon according to Billroth I, the biopsy specimen was obtained 40 cm from the gastroenterostomy, and in another (no. 2), operated upon according to Bill-

Table I. *Clinical and laboratory findings and appearance of small intestinal mucosa in patients with dermatitis herpetiformis*

Pat. no.	Sex	Age (y.)	DH duration (y.)	Height (cm)	Weight (kg)	Gastro-intest. sympt.	Faecal-fat excret (g/day)	5 h urinary xylose (g)	Haemo-globin (g per 100 ml)	Serum folate (ng per ml)	Whole blood folate (ng per ml)	Serum B_{12} (pg per ml)	FIGLU in urine (μM per hour)	Small intestinal mucosal appearance
1	♂	73	18	164	58	+	2.7	1.9	9.9	1.4	163	190	—[a]	Villous
2	♂	56	8	166	63	+	1.8	1.9	11.6	—	—	330	6	Villous
3	♂	42	11	166	71	0	4.3	0.8	13.4	1.9	83	450	10	Flat
4[b]	♂	45	8	178	72	0	10.3	2.2	12.0	1.7	46	290	24	Villous Flat Flat
5	♂	59	28	170	58	+	3.3	1.9	12.8	3.3	65	155	—	Convoluted
6	♂	50	21	173	86	0	6.6	1.9	12.2	1.7	75	460	19	Flat
7	♂	65	20	173	68	0	6.5	1.1	7.6	2.3	56	200	20	Villous
8	♀	25	13	178	53	0	9.6	1.7	11.6	2.0	56	—	16	Partly flat, partly convoluted
9	♂	68	17	174	61	+	14.0	0.8	8.8	1.4	—	860	39	Flat
Normal values							< 5.0	> 1.3		2.8–3.5	40–150	150–900	< 20	

[a] —= not analysed. [b] before diet.

roth II, from the upper part of the jejunum (the efferent loop).

The biopsy specimens were divided in three pieces. One was mounted on a plastic net and immersed in 4% formaldehyde for histologic examination. The other two pieces were immediately frozen in dry ice for measurements of disaccharidase and dipeptidase activities. Disaccharidases were determined according to Dahlqvist (5) and dipeptidase activities according to Josefsson & Lindberg (13) and Lindberg et al. (15). Unless otherwise stated each of the patients was examined by all methods used.

RESULTS

History and clinical observations (Table I). Two patients had undergone gastric resection. One of them (no. 1), who had been operated 20 years previously because of duodenal and gastric ulcers, complained of flatulence and mucus in the stools. The other (no. 2) had 9 years previously been operated because of duodenal ulcer. Since then he had had no symptoms related to the digestive tract. One patient (no. 5) had 15 years earlier had a long spell of diarrhoea. A fourth (no. 9) was admitted in a poor general condition after having been troubled for several months by vomiting and loose stools. Five of the patients had no gastrointestinal symptoms.

One patient (no. 8) was underweight and one (no. 6) was overweight. The others did not deviate appreciably from ideal weight (7).

X-ray examination of the stomach and intestine showed a normal postoperative appearance in cases 1 and 2 and only one patient (no. 9) showed pathological changes of the small bowel with alternating strictures and dilatations of the intestinal lumen. Superior mesenteric arteriography was done in four of the patients (nos. 2, 6, 7 and 9). The results of these examinations will be the subject of a separate paper (4).

Hematological findings. All patients except no. 3 had a hemoglobin value of < 13.0 g/100 ml; in five the anemia was mild, and in three (nos. 1, 7 and 9) more pronounced with hemoglobin values of 9.9, 7.6 and 8.8 g/100 ml. The serum iron was between 25 and 75 μg/100 ml in these three patients and in no. 4. Three of the patients with sideropenia showed an increased TIBC while in one (no. 9) TIBC was only 200 μg/100 ml. This patient had pronounced hypoproteinemia with a serum albumin of 1.8 g/100 ml.

The sternal marrow was examined in all patients except no. 3. An increased erythroid myeloid ratio was noted in three patients (nos. 2, 6 and 8). No megaloblasts were seen in any of the cases.

All patients showed signs of hemolysis. In seven the haptoglobin was decreased, 2–24 mg/100 ml. Reticulocytes were in all patients at least on one occasion more than 1.6%.

Table II. *Histologic appearance and disaccharidase activities (units per gram protein) of small-intestinal mucosal biopsy specimens from patients with dermatitis herpetiformis*

Patient no.	Appearance	Maltase	Isomaltase	Saccharase	Trehalase	Lactase
1	Villous	293	73	67	17	42
2	Villous	143	43	51	11	14
3	Flat	0	0	0	0	0
	Villous	263	92	75	24	3.3
4[b]	Flat	18	4.6	5.0	0.8	0.8
	Flat	62	18	15	3.0	2.2
5	Convoluted	—[a]	—	—	—	—
6	Flat	25	8.6	6.4	1.4	0.6
7	Villous	170	39	41	20	40
8	Partly flat, partly convoluted	67	18	18	3.5	7.4
9	Flat	108	30	28	2.3	7.6
Controls, mean value ($n=9$)		322	69.5	63.7	23.0	23.2
(range)		(126–446)	(31.4–142)	(33.6–148)	(10.9–36.3)	(8.7–36.3)

[a] — = not studied. [b] before diet.

Serum B_{12} was normal in all of the eight patients examined. The serum folate was between 1.4 and 2.3 ng/ml in six patients. The remaining two had normal values. FIGLU was analysed in eight patients and was increased in two of them: no. 4 excreted 24 μM FIGLU/hour and no. 9 excreted 39 μM/hour.

Absorption studies. All subjects showed a normal Schilling test. D-xylose absorption was abnormal in three patients (Table I).

Faecal fat excretion was increased in five patients (Table I). It was normal in the two patients who had undergone gastric resection.

Peroral biopsy of small-intestinal mucosa (Tables I, II and III). In seven of the patients only one mucosal biopsy was performed. In patient no. 3 two biopsies were taken with an interval of two months with the patient on a normal diet and the same medicamental treatment on both occasions. In patient no. 4 four biopsies were performed, two before, one after four months and the fourth after nine months of treatment with gluten-free diet.

In Table I the mucosal changes are classified morphologically in accordance with Shuster et al. (23). Severe enteropathy corresponding to what

Table III. *Histologic appearance and dipeptidase activities (units per mg nitrogen) of small-intestinal mucosal biopsy specimens from patients with dermatitis herpetiformis*

Patient no.	Appearance	Glycyl-L-leucine	L-Alanyl-L-glutamic acid	L-Glutamyl-L-valine	L-Alanyl-L-proline	Glycyl-L-glutamine[a]
1	Villous	304	56.6	30.9	17.4	—[b]
2	Villous	233	42.7	22.2	8.2	—
3	Flat	—	—	—	—	—
	Villous	170	23.5	9.7	7.7	50.3
4[c]	Flat	41	7.5	0	1.0	16.3
	Flat	136	26.2	7.7	1.2	49.7
5	Convoluted	—	—	—	—	—
6	Flat	72	19.8	0.4	0.6	32.8
7	Villous	—	35.0	8.3	5.0	22.6
8	Partly flat, partly convoluted	132	34.5	11.3	5.2	52.8
9	Flat	82	23.4	4.8	1.6	28.7
Controls, mean value ($n=9$)		216	37.5	22.2	10.0	65.4
(range)		(182–328)	(26.3–52.5)	(16.6–35.3)	(8.0–16.0)	(37.4–110)

[a] 0.04 *M* aqueous solution was used as substrate. pH optimum 7.7 (Lindberg, unpublished observations).
[b] — = not studied. [c] before diet.

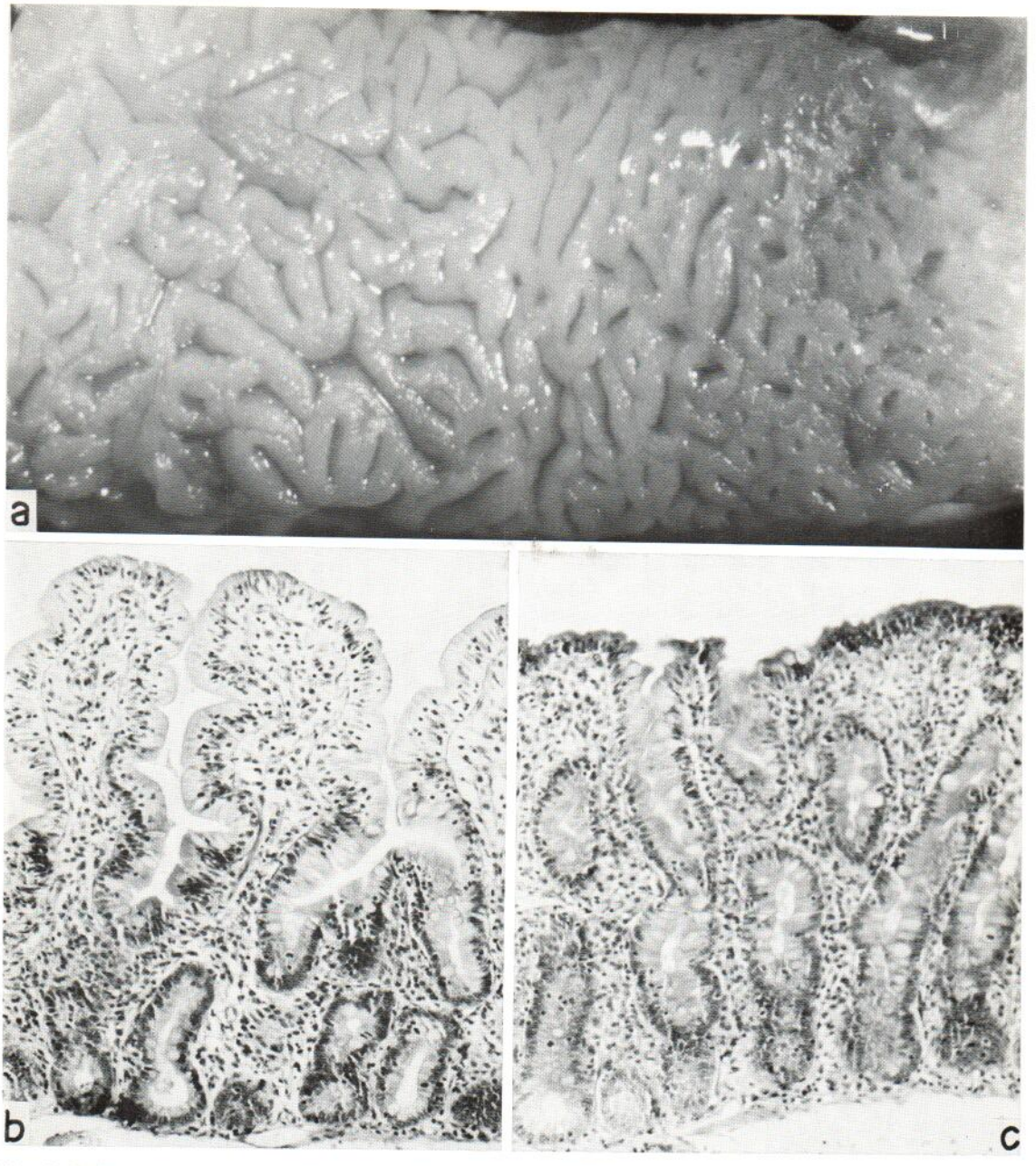

Fig. 1. Patient no. 8. The heterogenous picture of the mucosa from the duodeno-jejunal flexure is illustrated: (*a*) Appearance under the dissecting microscope with convoluted pattern to the left and flat mucosa to the right. (*b*) Low-power view of the convoluted part of the biopsy with distinct villous pattern and high columnar surface epithelium. (*c*) Low-power view of the flat mucosa. Note elongated crypts and low irregular surface epithelium.

is generally called partial or subtotal villous atrophy was seen in patients nos. 5, 6 and 9, in one of the biopsy specimens from patient no. 3 and initially in patient no. 4. Patient no. 8 showed a heterogeneous picture with severe changes in some areas and more preserved mucosa in others (Fig. 1). Two biopsy specimens (patients nos. 2 and 7) showed non-specific changes in the intestinal mucosa with atrophy of the type described by Foroozan & Trier (8). The biopsy from

patient no. 1 and the second biopsy from patient no. 3 were normal. All disaccharidases were abnormally low in the mucosal samples from patients nos. 6 and 8, the initial two biopsies from patient no. 4 and the first biopsy from patient no. 3 (Table II). In the second specimen from patient no. 3 only lactase deficiency was observed. In patient no. 9 all five enzyme activities were low but only trehalase and lactase were definitely abnormal. Disaccharidase activities were normal in patients nos. 1, 2 and 7.

Five dipeptidase activities were studied and the results are given in Table III. All five were definitely low in the first biopsy specimen from patient no. 4 and in nos. 6 and 9. In patient no. 7 the activity against L-alanyl-L-glutamic acid was normal while the activities against the other three dipeptides studied were decreased. The second biopsy specimen from case 4 and the one from patient no. 8 had both low activities against L-glutamyl-L-valine and L-alanyl-L-proline, slightly decreased activity against glycyl-L-leucine but normal activities against the remaining two dipeptides. The first biopsy specimen from patient no. 3 was not studied but the second had low activities against L-glutamyl-L-valine and slightly decreased activity against L-alanyl-L-glutamic acid. Normal dipeptidase activities were found in patients nos. 1 and 2.

In patient no. 5 the mucosal sample was too small to permit enzyme activity analysis.

When patient no. 4 had been on a gluten-free diet for four months the changes in the intestinal mucosa showed distinct regression with single plump, leaf-shaped villi but still abundant cellular infiltration. All five disaccharidases were normalized. After the patient had been on a gluten-free diet for 9 months the histological changes had regressed even more. The dipeptidase activities were, however, still significantly decreased (Table IV).

Table IV. *Histologic appearance and disaccharidase and dipeptidase activities of the small intestinal mucosa in patient no. 4 before and after treatment with gluten-free diet*

	Appearance	Maltase	Isomaltase	Saccharase	Trehalase	Lactase	Glycyl-L-leucine	L-Alanyl-L-glutamic acid	L-Glutamyl-L-valine	L-Alanyl-L-proline	Glycyl-L-glutamine[a]
Before diet	Flat	17.5	4.6	5.0	0.8	0.8	41	7.5	0	1.0	16.3
Before diet	Flat	61.5	18.2	15.2	3.0	2.2	136	26.2	7.7	1.2	49.7
After 4 months diet	Convoluted-villous	213	56.4	64.2	15.5	17.9	—[b]	—	—	—	—
After 9 months' diet	Villous	137	44.4	41.2	9.6	10.0	77	12.8	0	1.2	21.1
Controls, mean value	($n=9$) (range)	232 (126–446)	69.5 (31.4–142)	63.7 (33.6–148)	23.0 (10.9–36.3)	23.2 (8.7–36.3)	216 (182–328)	37.5 (26.3–52.5)	22.2 (16.6–35.3)	10.0 (8.0–16.0)	65.4 (37.4–110)

[a] 0.04 *M* aqueous solution was used as substrate. pH optimum 7.7 (Lindberg, unpublished observations).
[b] — = not studied.

DISCUSSION

Several authors have shown that intestinal dysfunction of the type seen in coeliac disease is common in dermatitis herpetiformis (9, 10, 16, 17, 23, 25). In a compilation of personal cases and other materials Shuster et al. found subtotal or partial "villous atrophy" in 50 of 83 patients with dermatitis herpetiformis (23). Such "disappear-

ance" of the villi was observed in six of our nine patients (Table I).

Subnormal disaccharidase activities were found in 7 out of 12 cases of dermatitis herpetiformis studied by Fraser et al. (9). In our group of eight patients studied, five showed subnormal disaccharidase values (Table II).

Hitherto no studies of the intestinal dipeptidases in dermatitis herpetiformis have been performed. In three of our patients all five dipeptidase activities studied were low. In three patients low activities were found against at least two of the dipeptides (Table III).

Thus, in our group of eight patients studied, only two were completely normal. These two had both undergone gastric resection.

Of the six biopsies with low dipeptidase activities four showed "disappearance" of the villi. Five of them had abnormal disaccharidase activities. Thus determination of the didpeptidase activity seems to be a sensitive test for small intestinal mucosal dysfunction in dermatitis herpetiformis as in gluten-induced enteropathy (15).

It is known that intestinal biopsy specimens obtained simultaneously from one and the same individual can show different pictures (21). In one of our patients some areas of the specimen showed severe enteropathy, while others had a more normal appearance (Fig. 1). In another patient biopsies with an interval of two months showed completely different histological pictures in spite of the fact that the diet or the therapeutic measures had not been altered. The findings in these two cases indicate that the bowel lesions may be patchy.

In all patients with steatorrhea the condition was only mild, an observation noted also in previous series of patients with dermatitis herpetiformis. It is therefore remarkable that when enzyme changes occurred in the intestinal mucosa they were as severe as in coeliac disease with its more pronounced symptoms of malabsorption. It is possible that the reason for milder symptoms in the enteropathy of dermatitis herpetiformis is that the intestinal changes are circumscribed. In coeliac disease the severity of the illness is related to the length of bowel injured (22).

In all of our nine patients there was some sign of gastrointestinal abnormality. In this conjunction it should, however, be pointed out that our cases were selected: only patients with dermatitis herpetiformis difficult to control or with anemia were examined.

In two patients who had undergone gastric resection dermatitis herpetiformis appeared 1 and 2 years after the operation. In one of the patients no intestinal changes at all were seen, while the other showed slight histological alterations. The enzyme activities in these two patients were normal. However, it should be pointed out that the biopsies were taken from the upper jejunum, where the enzyme activities normally are somewhat higher in comparison with those in the mucosa of the duodeno-jejunal flexure (3, 18).

Investigations of relatives of patients with dermatitis herpetiformis have revealed signs of enteropathy with or without symptoms (17, 23). A brother of our patient no. 5 had coeliac disease with typical intestinal biopsies but no dermatitis.

Treatment with gluten-free diet can improve the intestinal symptoms of coeliac disease both in patients with and without associated dermatitis herpetiformis (11, 19, 23). Fry et al. (11) registered improvement of the skin symptoms as well in patients with dermatitis herpetiformis and enteropathy, while Shuster et al. (23) found no evidence for gluten-free diet having an effect on the dermatosis.

Patient no. 4 was studied after he had strictly avoided gluten for 9 months. Already after 4 months a certain histological normalization was noted and the disaccharidases had become normal. Yet after 9 months of treatment with gluten-free diet the dipeptidases were still subnormal (Table IV). While on diet the patient had put on 5 kg and he felt much better. He had never before succeeded in gaining weight. His skin symptoms had, however, not been affected by the diet and still required sulfone treatment as before.

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