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GLUTEN-FREE DIET FOR DERMATITIS HERPETIFORMIS: THE LONG-TERM EFFECT ON CUTANEOUS, IMMUNOLOGICAL AND JEJUNAL MANIFESTATIONS

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Abstract. In 32 patients with dermatitis herpetiformis (DH) we studied the effect of gluten-free (22 patients) and gluten-reduced (10 patients) diet for periods ranging between 15 and 43 months. Variables such as cutaneous manifestations, dependence on dapsone, IgA deposits in the skin, small-bowel function, and jejunal mucosal morphology were studied. 59% of the patients on gluten-free diet could stop dapsone medication and remain symptom-free, compared with 10% on gluten-reduced diet. The time needed to achieve this therapeutic response varied from 5 to 31 months. IgA decreased in the skin to a degree which roughly paralleled the morphological normalization of the jejunal mucosa. In no patient, however, did the IgA completely disappear. It is suggested that IgA is not the main factor inducing DH symptoms, but rather a secondary phenomenon. Repeated jejunal biopsies revealed normalization of the mucosal histology in 52% of the patients on gluten-free diet, compared with none in the gluten-reduced diet group.

Key words: Dermatitis herpetiformis; Gluten-free diet; Skin IgA; Jejunal mucosal atrophy

The cause of dermatitis herpetiformis (DH) is still unknown. There are two main areas of interest in the pathogenesis of the disease. One is the deposition of IgA in both normal-appearing and perilesional skin of patients with DH (15), a feature which has been considered a prerequisite for the diagnosis (9). The second area is the morphological and functional changes of the small intestine similar to those found in coeliac disease (7, 13, 21), and the fact that gluten-free diet improves the enteropathy of DH as well as diminishing the skin manifestations (6, 17).

The aim of the present investigation was to study the long-term effect of gluten-free diet on the skin changes, the requirements for dapsone medication, the deposition of immunoglobulins in the skin and the intestinal mucosal changes and function.

MATERIAL AND METHODS

Diagnostic criteria and selection of patients

The criteria of DH used were: (*a*) clinically severe itching and symmetrical pleomorphic erythematous, papular and/or vesicular often excoriated skin lesions predominantly on extensor surfaces of the arms and legs, the scapular areas, the buttocks and hips; (*b*) histopathologically a predominantly neutrophilic and eosinophilic inflammatory cell infiltrate forming microabscesses and the formation of subepidermal vesicles at the tip of dermal papillae; and finally (*c*) prompt therapeutic effect of dapsone and a similarly rapid reappearance of itching and skin lesions after withdrawal of dapsone.

Thirty-two patients fulfilling the criteria of DH treated at the Department of Dermatology, Linköping University Hospital, were included in the present series. Selection of the patients concerned was as follows: All 85 patients with the diagnosis of DH recorded at the department during 1971-75 were scrutinized as regards the diagnostic criteria of DH. Fifty-seven fulfilled the criteria and were alive and still lived within the region. Fourteen patients agreed to start gluten-free diet. Of the patients excluded from the study, 16 had already started gluten-free diet but had not been examined according to our requirements, 4 had other concomitant diseases and 23 (12 of whom were more than 70 years of age) were unwilling to attempt the diet. During the next 3-year period, 1976–78, 26 patients attending the department fulfilled the criteria of DH, and 18 of them were included in the present series. Two patients were already on diet instituted at other clinics. The remaining cases were excluded due to old age (4 cases) and a negative attitude to the diet.

Of the 32 patients thus selected for the investigation 27 were males (84%) and 5 were females. The mean age was 49 years (range 22–71) and the mean duration of the disease prior to the institution of diet was 8.5 years (range 0–27). As a comparison 35 (69%) of the 51 cases not included in the present investigation were males and 16 females; the mean age was 57 years (range 10–83 years).

Investigation before introduction of diet

All patients were clinically examined at the Department of Dermatology and the Gastroenterology Division of the Department of Internal Medicine. Symptoms from the gastrointestinal tract were specifically enquired after.

Immunofluorescence in skin biopsies

Skin biopsies from apparently normal skin taken from the upper dorsal part of the arms were snap frozen in liquid nitrogen for immunofluorescence studies. Deposits of human IgA, IgG, IgM, C3 and fibrinogen were stained by applying appropriate FITC-conjugated antisera (Wellcone Ltd) to unfixed 3 μm cryostat sections (4).

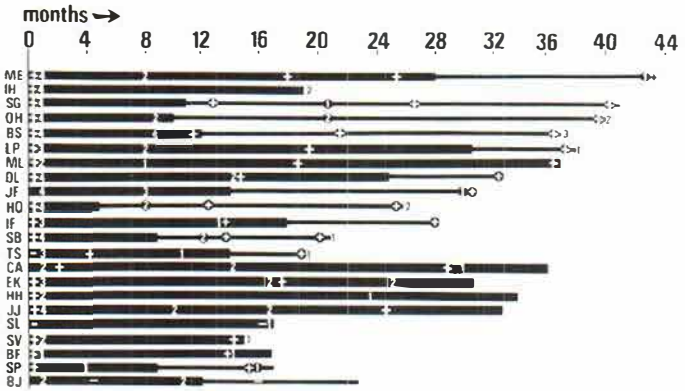

Fig. 1. Effect of strict gluten-free diet in 22 patients with dermatitis herpetiformis on clinical skin manifestations, cutaneous immunofluorescence and jejunal histopathological biopsy finding. Skin: ——, no itching or lesions without dapsone medication; ▬, skin manifestations. Immunofluorescence: +, deposition of IgA in a granular pattern in the basal membrane of the skin; −, no deposition of IgA. Jejunal biopsy: grading according to Alexander (1): 1, normal (I); 2, slight but significant (II); 3, moderate (III); 4, severe (IV) crypt hyperplasia, villous atrophy, enterocyte changes and mucosal inflammatory cell infiltration.

Microscopy was carried out with a Zeiss incident light fluorescence microscope. The amount of IgA deposited in the skin was graded according to the percentage of the basement membrane (BM) covered by granular IgA deposits: IV = 100% of BM ("granular band"), III = 50–100% of BM, II = 10–50% of BM, I = 0–10% of BM and 0 no detectable deposits. Further, the extremes of depth of IgA "granular band" deposits were designated as thick and thin. Deposits in the dermal papillae and along fibres in the dermis were not quantitated in this study.

Biopsies taken from the same patient at different times and stored at −70°C were compared on the same occasion by two investigators who did not know which of the biopsies was taken first. Re-evaluation could be performed in only 19 cases, since some specimens were destroyed during storage.

Laboratory investigations

The following blood tests were done, using standard laboratory techniques: Haemoglobin, R.B.C., reticulocytes, W.B.C., differential count, thrombocytes, serum iron, total iron-binding capacity, albumin, creatinine, bilirubin, liver enzymes, serum folate, vitamin B12, immunoglobulins, electrolytes including sodium, potassium, calcium, magnesium, zinc and phosphorus. The urine was examined for albumin, glucose and haemoglobin.

The first 24 patients were also hospitalized and examined with the following tests for small bowel function: Faecal fat excretion according to van de Kamer with 3 days' collection on a 10 g/24 h fat intake, 25-g oral D-xylose test using a timed 5-hr urine excretion, lactose tolerance test after administration of 50 g lactose orally, vitamin B12 absorption without and with intrinsic factor, and urinary indican excretion.

Jejunal biopsy

A single intestinal mucosa biopsy was taken from the duodenojejunal junction using a Watson capsule. The position of the capsule was controlled fluoroscopically. The initial biopsy failed in one patient for technical reasons.

The specimens were fixed in 4% formaldehyde. They

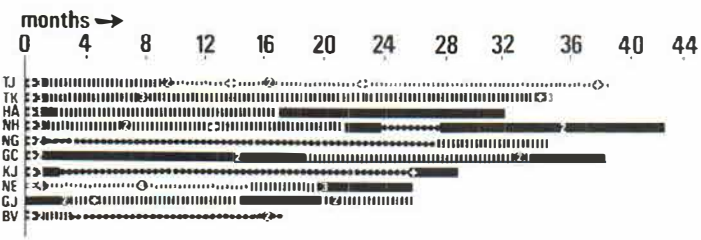

Fig. 2. Effect of gluten-reduced diet in 10 patients with dermatitis herpetiformis on clinical skin manifestations, cutaneous immunofluorescence and jejunal histopathological biopsy findings. ▬, periods of strict gluten-free diet and skin manifestations; ▪▪▪▪▪▪▪▪▪▪, periods of gluten-reduced diet and skin manifestations; ▪▪▪▪▪▪▪▪▪▪, periods of gluten-reduced diet and no skin manifestations without dapsone; ——, no diet (normal diet) and skin manifestations. Immunofluorescence: + −, and jejunal biopsy 1–4, see caption to Fig. 1.

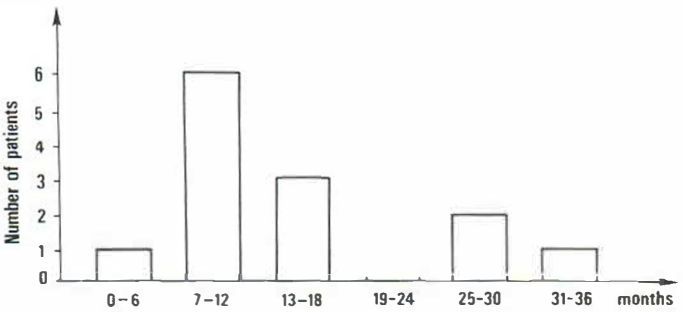

Fig. 3. Duration of strict gluten-free diet in 13 patients with DH prior to freedom from skin symptoms without dapsone medication.

were examined under the stereo-microscope whilst still immersed in the fixative. The specimens were embedded in paraffin wax. Sections approximately perpendicular to the surface and about 4 μm thick were cut. They were stained with haematoxylin-eosin, haematoxylin–van Gieson and the periodic acid–Schiff reaction was performed. The specimens were examined with regard to alterations characteristic of coeliac disease and classified according to Alexander (1), considering both the stereological and histological features. Grade I is normal and Grades II–IV represent an increasing degree of injury to the mucosa.

Gluten-free diet

All patients were carefully informed about the gluten-free diet by the same two dieticians who also invited the patients to contact them if there were any problems with the diet during the study.

At the end of the study the patients were divided into two groups. Those who had adhered strictly to the recommended gluten-free diet throughout the whole of the observation time are referred to as the gluten-free diet group (n=22) and those who had admitted some gluten intake part of the time or during the whole study are included in the gluten-reduced diet group (n=10).

Follow-up

The patients were regularly seen by the same doctor (mostly T. F. or L. M.) at the Department of Dermatology every second to third month. On these occasions the presence of itching and skin lesions, symptoms from the gut and the requirement for dapsone were registered. Biopsies for immunofluorescence were mostly performed after the patients were free from skin symptoms without dapsone medication and thereafter every year. The first jejunal biopsy control was taken within one year after entering the study in 29 of the 32 patients. Two patients refused another jejunal biopsy and one patient moved temporarily to another part of the country. These 3 patients were in the gluten-reduced diet group. The biopsy was repeated every year until the mucosa was histologically normal, and in some cases also after normalization.

RESULTS

Skin manifestation

Twenty-two patients were on strict gluten-free diet during a follow-up period of 15 to 43 months. Fig. 1 shows the individual observation time and the withdrawal of dapsone medication without relapse. During this follow-up period 13 of the 22 patients (59%) could stop the dapsone medication and remained free from skin symptoms. One patient became symptom-free within 6 months, 6 patients within one year and in 3 it was more than 2 years before they were free of symptoms (Fig. 3).

The 9 patients still on dapsone and gluten-free diet have been followed for 15 to 37 months (Fig. 4). Four of them with an observation time of 37, 33, 17 and 15 months respectively, were much improved and could reduce the dapsone dose to less than 25% of the initial requirement.

Only one of the 10 patients on gluten-reduced diet could stop dapsone medication without recurrence of skin symptoms and another one could reduce the

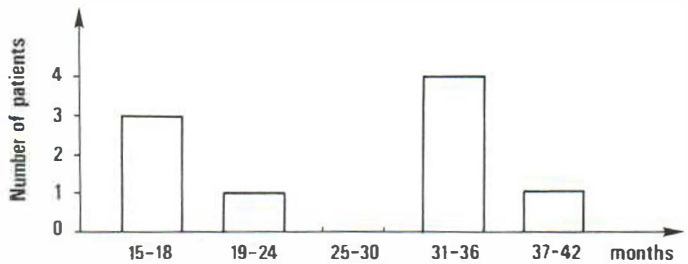

Fig. 4. Observation period of 9 patients with DH on strict gluten-free diet still requiring dapsone medication.

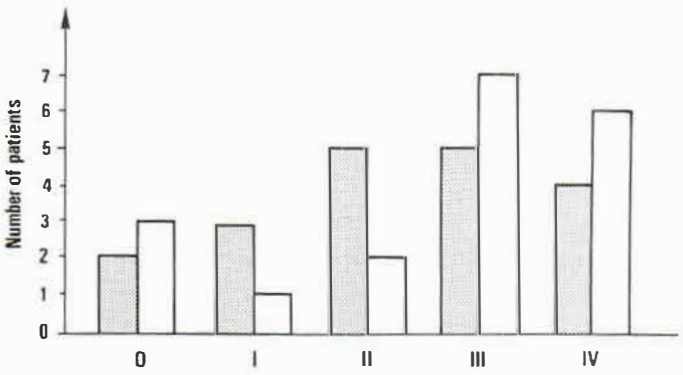

Fig. 5. IgA fluorescence along the basement membrane in skin (for grading, see methods) in 19 patients at the start of the study (□) compared with the latest biopsy (⊠).

dose to less than 25% (Fig. 2). All but one of the patients in this group were followed for more than 2 years.

IgA deposits in uninvolved skin

Granular deposits of IgA along the basement membrane of uninvolved skin were detected by direct immunofluorescence in all but 2 of the 32 patients (Figs. 1 and 2). The deposits of IgA were still present at all re-examinations even if the patients were free of symptoms from the skin and had been able to withdraw dapsone. A small decrease in IgA deposits along the basement membrane could be disclosed by a careful comparative examination of skin biopsies taken on different occasions (Fig. 5). This decrease seemed to parallel the normalization of the jejunal mucosa (Table I).

Of the 16 individuals presented in Table I, 13 were in the gluten-free diet group and 7 of them showed a decreased fluorescence as compared with none of the 3 patients in the gluten-reduced diet group.

Gastrointestinal symptoms

Symptoms from the gastro-intestinal tract were spontaneously reported by 12 of the 32 patients (38%). Six patients had previously seen a doctor solely because of their gastro-intestinal complaints and 3 of them had been hospitalized due to acute abdominal symptoms. The other 6 patients considered their symptoms to be of minor degree. Only after direct questioning did another 8 patients (25%) admit abdominal complaints, such as diarrhoea, meteorism, borborygmi and flatulence. The remaining 12 patients (38%) denied any symptoms whatsoever from the gastro-intestinal tract.

We found no relationship between gastro-intestinal symptoms and jejunal biopsy findings. Seven of the symptom-free patients had severe mucosal changes (grades III or IV) and 5 had mucosal changes of grade II.

Laboratory investigations

Table II shows the results of the tests of gastro-intestinal function performed in the 24 patients first entering the study. 50% had steatorrhoea and only 3 of the 11 patients with advanced microscopic mucosal changes (grade IV) had normal values for faecal fat excretion. 11 of 22 patients examined had a decreased urinary D-xylose excretion, and 9 had concomitant steatorrhoea. Three of 10 patients with grade IV mucosal changes had a normal D-xylose test but 2 of those 3 patients had steatorrhoea.

The 10 patients with low serum folate values had repeated serum folate controls. Seven of those patients adhered strictly to the gluten-free diet and their serum folate values normalized without substitution, whereas the 3 patients on gluten-reduced diet needed constant maintenance therapy to keep their serum folate value within the normal range.

Table I. *Relationship between the jejunal mucosal alterations and the amount of IgA fluorescence in the skin of the same patients*

Histological grading of jejunal mucosa according to Alexander (1)

	Jejunal biopsy		
IgA fluorescence	IV, III or II →I	IV or III →II	IV→III or no change
Decreased	4	3	0
No change	2	1	3
Increased	1	2	0

Table II. *Per cent abnormal tests for small bowel function in 24 patients with DH prior to gluten-free diet*

Small bowel function test	Abnormal test (%)
Serum folate	38
Serum B12	0
Faecal fat	50
D-xylose excretion	50
Lactose tolerance test	13
Indican excretion	25

Table III indicates the good correlation between pathological small-bowel function tests and jejunal mucosal abnormalities at biopsy.

We are in progress with further investigations concerning functional aspects on the gastro-intestinal involvement in these cases which will be reported on separately.

Jejunal morphology

The jejunal biopsy findings before diet are shown in Figs. 1 and 2. Slight but definite abnormalities (grade II) were found in 9 cases (29%), more advanced changes grades III and IV in 8 (26%) and 11 (35%) respectively. The biopsy was judged as normal in 3 (10%).

Control biopsies in 21 of the 22 patients on strict gluten-free diet revealed histological improvement in 18, of whom 11 obtained a microscopically normal mucosa. The remaining 3 patients showed the same mucosal morphology as before diet; 2 were normal (grade I) from the outset and one still had grade II changes one year after starting on diet.

Seven of the 10 patients on gluten-reduced diet were re-examined and 3 improved but none reached full normalization of the mucosal histology. The relationship between skin symptoms and intestinal morphology is given in Table IV, showing a relationship between improvement of jejunal mucosa and disappearance of cutaneous manifestations. In contrast to strict gluten-free diet a reduction of gluten in the diet resulted neither in normalization of the jejunal mucosa nor cutaneous symptomlessness.

Table III. *Small bowel function tests in relation to jejunal mucosa morphology in 24 patients with DH prior to gluten-free diet*

Small bowel function test	Jejunal mucosa histology[a]			
	I	II	III	IV
All tests normal[b]	1	1	1	1
One test pathological		3	2	1
Two tests pathological			3	4
Three or more tests pathological			2	5

[a] Grading according to Alexander (1).
[b] See Table II.

Table IV. *The effect of diet on jejunal biopsy findings in relation to skin manifestations in 26 patients with DH, 19 on strict gluten-free diet and 7 on gluten-reduced diet*

Clinical grading: No symptoms = without dapsone medication, much improved = reduction of dapsone medication to less than 25% of initial requirement without symptoms. Histological grading of jejunal mucosa according to Alexander (1)

Skin manifestations,	Jejunal biopsy		
	IV, III or II →I	IV or III →II	IV→III or no change
Strict gluten-free diet			
No symptoms	7	3	2
Much improved	3	0	0
No change	1	3	0
Gluten-reduced diet			
No symptoms	0	1	0
Much improved	0	0	1
No change	0	1	4

DISCUSSION

Dermatitis herpetiformis (DH) has been coupled to coelic disease and considered, like coeliac disease, to be due to gluten sensitivity (6, 23). This investigation, in agreement with several other studies (6, 8, 14), has shown that gluten-free diet can affect the skin disease favourably. Strict diet is significantly more effective than gluten-reduced diet ($p<0.05$).

The result of the present study shows that the effect of gluten-free diet on the skin symptoms is a late effect. Only one patient was free of symptoms within 6 months on the diet and some were not free until after 2 or 3 years' dieting. Weinstein et al. (24) obtained no improvement in the skin manifestation of DH as a result of treatment with gluten-free diet for up to 6 months despite a sttiking improvement in

jejunal villous architecture. It is, thus, impossible to fully evaluate the efficacy of gluten-free diet until after a considerable period of time.

We have been unable to show which is the most important cause of the varying response to gluten-free diet. Despite the parallelism between the mucosal improvement and the disappearance of the cutaneous manifestations, 1/3 of the symptom-free patients still showed jejunal abnormalities. In the symptom-free patients an abnormal jejunal mucosa does not usually result in DH symptoms when they are exposed to dietary substances other than gluten, which indicates the central role of gluten in the process resulting in the cutaneous manifestation of DH. This central role of gluten is also supported by the demonstration of membrane-bound vacuoles in the dermis subjacent to the basement membrane in patients symptom-free on dapsone medication but not in patients symptom-free on gluten-free diet (17).

The effect of dapsone may be explained by its ability to block inflammatory mediators of granulocytes, thus merely suppressing the pathological process so that it does not become clinically manifest (22).

The finding of IgA in the skin of coeliac patients with DH but not in coeliac patients without DH has been taken as an indication of the role of IgA as a pathogenic factor in the induction of the skin manifestation. The IgA deposits in the skin are thought to originate from the diseased gastro-intestinal tract (12, 20).

Our results show that the demonstration of IgA in normal skin is a sensitive test for the diagnosis of dermatitis herpetiformis and a good diagnostic aid especially in cases where the diagnosis is otherwise uncertain.

Unlike Fry & Seah (9) we do not consider IgA to be an absolute prerequisite for the diagnosis of DH, since 2 of our cases were IgA-negative and one was initially IgA-negative. Another patient not included in this series also lacked IgA in the skin in the first biopsy. For patients having a clinical picture strongly suggestive of DH but lacking IgA in the initial biopsy, the importance of serial sections (3) and repeated biopsies (19) has been stressed.

In the present investigation a decrease in skin IgA deposits was established in patients on gluten-free diet but no patients became IgA-negative during the observation period of up to 43 months. The decrease was small but correlated to the normalization of the jejunal mucosal morphology and probably reflects normalization of the mucosal barrier with a decrease in IgA-producing plasma cells (16) and circulating IgA. We could not, however, find any correlation between the amount of IgA deposits and the severity of symptoms prior to diet. This speaks against the assumption that IgA is the dominant factor in inducing DH symptoms. Harrington & Read (11) showed that the concentration of IgA in the skin falls within 6 months of gluten withdrawal. In 2 of their patients IgA disappeared entirely, which they found to suggest a central role for IgA in the generating of skin lesions. Recently Salo & Reunala have shown the disappearance of IgA in some patients on gluten-free diet about 3 years after they became free from symptoms (18). These results could not be verified by Fry et al. (10) who found no difference in the quantity of IgA in the skin of patients on gluten-free diet and without symptoms for up to 7 years.

It is not known whether IgA in the skin of DH-patients has reactivity (of immunological or non-immunological nature) to some skin constituent (normal or abnormal) or whether it is deposited as immune complexes. The difficulty in eluting IgA (5) from the skin at low pH and the absence of glomerular engagement in the DH-patients makes an autoimmune or immune complex mediated disease a less likely explanation. The presence of IgA deposits seems rather to be a secondary phenomenon of low pathogenetic significance.

We think that serum folate, D-xylose test and faecal fat excretion are useful biochemical parameters in detecting enteropathy in DH patients. Jejunal biopsy provides proof of the intestinal abnormality. The high percentage of pathological jejunal biopsy findings in the present investigation despite single jejunal biopsy technique indicates that the patchy distribution of villous atrophy previously suggested (2) is probably not the predominant pattern. However, one patient with a normal first jejunal biopsy still became free from skin lesions on gluten-free diet and in this case we perhaps missed a patchy atrophy. Thus, even in a patient without intestinal abnormality demonstrated at a single jejunal biopsy, gluten-free diet is worth trying if the diagnosis of DH is established.

As shown in the present investigation a large proportion of the patients with DH can be cured in the skin as well as in the gut by strict gluten-free diet, while dapsone therapy only suppresses the

skin symptoms. Dapsone therapy is usually effective and comfortable for the patient, while gluten-free diet often constitutes a major upheaval in the patient's way of life. On the other hand, lifelong dapsone therapy involves a risk of side effects. Gluten enteropathy implies a potential risk of metabolic effects of malabsorption such as anaemia, osteoporosis, etc. and perhaps an increased risk of intestinal lymphoma. For these reasons it is our firm belief that at least young patients and those with signs of malabsorption should be strongly encouraged to adopt a gluten-free diet.

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