

## Spontaneous Remission of Dermatitis herpetiformis: Dietary and Gastrointestinal Studies

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Out of 98 patients with dermatitis herpetiformis (DH) living in Gothenburg, 14 were in spontaneous remission (29% of the patients without glutenfree diet). Eight of these volunteered for dietary interviews and further studies. They do not seem to differ from symptomatic DH patients in the frequency of HLA-B8, achlorhydria or small-bowel enteropathy. Their estimated mean daily intake of gluten was below 12 g in six. The mean gluten intake of the eight patients in remission is significantly less than in a group of 34 patients with dapsone-requiring DH on non-restricted diet. Urinary iodine excretion was low in five, all previously instructed to restrict their iodine intake. Dietary factors could thus be suspected to be responsible for some spontaneous remissions in DH. *Key words: Gluten intake; Iodine intake.* (Received September 26, 1985.)

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Dermatitis herpetiformis (DH) has been considered a chronic disorder although some variation in disease activity may occur, as is evidenced by the variation of the dose of dapsone required to control the skin eruption (1, 2). However, spontaneous complete remissions have been considered rare in DH (1). Moreover, some of the remissions reported by early authors may have been due to inaccurate diagnosis, e.g. difficulties in separating bullous pemphigoid from DH. In recent years the rising interest in DH has in some places led to a concentration of cases to special DH outpatient clinics jointly run by dermatologists and gastroenterologists. It has thereby become apparent that a few patients without pharmacological or dietary treatment may indeed experience a long-standing remission free from itching and skin lesions. There are only a few reports on the number of patients in spontaneous remission, with divergent results. Thus, in the US 2 of 32 (6%), in England 2 of 25 (8%) and 5 of 36 (14%) and in Sweden 16 of 37 (43%) patients on a normal diet experienced a natural remission (2-5). In these studies IgA-positive skin deposits were required for the initial diagnosis of DH.

The reasons why some patients remit are unknown. Both the skin lesions and the enteropathy are gluten-dependent and long-term gluten withdrawal clears the skin lesions and tends to normalize the enteropathy (6). Utilizing a dietary history method, we have calculated the mean daily intake of gluten of 45 IgA-positive DH patients in Sweden to be 15 g, corresponding to the average national gluten intake (7). We found a significant correlation between the degree of morphological mucosal changes of the small intestine and the quantity of gluten ingested. To be effective in controlling the skin lesions, it is recommended that the GFD is strict (2). A gluten-restricted diet may, however, be beneficial although it induced significantly fewer remissions than GFD (2, 8). It cannot be excluded that spontaneously remitting patients in fact have a low gluten intake. Moreover,

it has been speculated that other dietary factors than gluten may contribute to the skin lesions by crossing the abnormally permeable intestinal mucosa (9). Iodides, administered orally or topically, can provoke DH-like skin lesions (1). Previously, DH patients were therefore often recommended to restrict their dietary iodine intake. The role of dietary iodine in the development of skin lesions in DH has, however, not been clarified.

The aim of this investigation was to determine the incidence of spontaneous remission in DH patients on a normal diet, and to study their gluten consumption (calculated from dietary history interviews) and iodine intake (estimated from urinary excretion) and some gastrointestinal functions.

## PATIENTS AND METHODS

### *Patients*

In a previous study of the epidemiology of DH, patients were collected from the city of Gothenburg with a population in 1981 of 428 171 inhabitants (10). An exhaustive search for patients was made. On December 31, 1981, there were 98 patients with DH known to be living in the city. The diagnosis, suspected from the clinical picture and histological appearance of skin lesions, was in all cases verified by the presence of granular IgA deposits in dermal papillae of uninvolved skin (11). Patients taking dapsone regularly tried to adjust the dose to the lowest effective level.

Of these 98 DH patients, 14 (10 females) were in spontaneous remission on December 31, 1981, i.e. they had had no skin lesions during the preceding 6 months in spite of adhering to their ordinary diet and not taking dapsone. Since 35 patients on a normal diet had dapsone, 29% of the patients without GFD were in remission.

Eight patients with spontaneous remission volunteered for further studies (four men and four females). The mean age of onset was 43 years (range 8–74) and the mean duration of disease 19 years (range 4–39). A new skin biopsy was obtained in these patients. All patients still had granular IgA deposits in the upper dermis.

Their skin symptoms were mild from onset and four patients had never required dapsone. Another two patients had discontinued dapsone therapy several years earlier. The remaining two patients had required less than 10 dapsone tablets (each containing 0.1 g) during the previous year.

### *Dietary interviews*

The same dietitian (KF) performed all interviews on food habits. A dietary history method including cross-checking using a special questionnaire was used (12, 13). The patients were interviewed in detail about their dietary habits. For every food item, the patient was asked about the frequency of consumption (per day, week or month) and also about the size of the portions in order to estimate the average daily consumption. Individual intake of energy, protein, carbohydrates, fat and iron was calculated from food consumption tables (Swedish National Food Administration, 1978). The intake of dietary fibre was calculated from data reported from different laboratories (Southgate, Englyst, Asp, Sandberg) using a macrodata system.

Gluten intake was especially scrutinized in the interviews. Based on analyses of different flours (Product Development Laboratory, Kvarn och Bageri AB, Juvel), the gluten content was calculated to be 80% of cereal protein. Oat consumption was not included in the calculation of gluten.

For comparison of the dietary intake of DH patients on dapsone treatment, the results of 34 interviews published previously were used (7).

### *Iodine in urine*

One 24-h urine collection was made in seven patients. One patient was not willing to collect urine. After measurement of the volume, a sample was deep-frozen for subsequent analysis. Iodine was assayed according to Sandell & Colthoff (14) and Sachs (15) by the Swedish National Food Administration. The daily mean iodine urinary excretion in a group of healthy Swedish control subjects was 1.76  $\mu\text{mol/day}$  for the males and 1.61  $\mu\text{mol/day}$  for the females (16).

### *HLA determination*

HLA typing was performed by the lymphocytotoxic microtechnique as previously outlined (17).

### *Gastrointestinal examinations*

Maximal gastric acid secretion was determined during nasogastric intubation after subcutaneous stimulation with pentagastrin, 6  $\mu\text{g/kg}$  bodyweight (18). Achlorhydria was defined in accordance with

Callender et al. (19). Small bowel mucosal biopsies were obtained either endoscopically from the second part of the duodenum and/or as capsule biopsy from the duodenojejunal junction (18). The classification was based on the dominant finding in this group of biopsies. Small-bowel mucosal findings were graded as normal, inflammatory reaction only, partial villous atrophy, or subtotal villous atrophy (18).

#### *Gliadin antibodies*

Serum gliadin antibodies of the IgA and IgG classes were determined by diffusion-in-gel enzyme-linked immunosorbent assay (DIG-ELISA) as previously described (20). The antibody levels correlated with the severity of the enteropathy (20). Diameters exceeding 11.4 mm in the IgA gliadin antibody assay and 13.6 mm in the IgG gliadin antibody assay were considered to represent a significantly increased level of gliadin antibodies (20).

## RESULTS

### *HLA*

HLA-A1, B8 occurred in 5 of the 8 patients (Table I).

### *Gastrointestinal examinations*

Achlorhydria occurred in two out of five patients. In addition, one patient had had a gastric resection for carcinoma.

Increased IgG and/or IgA gliadin antibody titres occurred in 5 patients. During this study, intestinal biopsies were obtained in two patients. One had subtotal villous atrophy (B. N.) and the other a normal mucosa (E. A.). Based on intestinal morphology and serology, 5 of 8 patients thus had proven or probable enteropathy at the time of the dietary interview. Small intestinal biopsies had been obtained during 1976–1980 in 4 patients who then already had very mild skin symptoms. Three had had subtotal villous atrophy (P.-E. W., D. O., E. H.) and one had a normal mucosa (G. J.).

### *Gluten intake*

All patients were aware that GFD reduces the skin and intestinal lesions of DH. Three of them had previously tested a GFD for a maximum of 6 months. They defaulted because of

Table I. Details of eight patients with dermatitis herpetiformis in spontaneous remission

ND = not done

Patient	Sex	Age at onset	Duration of disease (yrs)	HLA-B	Gliadin antibodies (mm)		Achlorhydria	Gluten intake (g/day)	Iodine excretion ( $\mu$ mol/day)
					IgA	IgG			
P.-E. W.	M	8	20	—	9	11	—	12.8	1.64
G. J. <sup>a</sup>	F	56	19	+	13	17	+*	11.1	1.23
D. O. <sup>b</sup>	M	35	6	+	12	15	—	10.3	1.01
B. K.	M	43	29	+	14	20	ND	6.2	0.73
B. N.	M	26	39	+	13	17	+	18.5 <sup>c</sup>	1.15
E. A.	F	50	4	—	7	12	—	9.7	1.24
G. H.	F	74	7	—	9	11	ND	8.7	1.34
E. H.	F	50	24	+	13	15	+	9.1	ND

<sup>a</sup> Diabetes mell., pernicious anaemia, partial gastric resection due to gastric carcinoma, temporal arteritis, status post cerebrovascular lesion.

<sup>b</sup> One daughter has coeliac disease.

<sup>c</sup> Loose stools last 6 months.

weight reduction (2 cases) and/or loss of motivation (2 cases). One patient (G. J.) followed dietary prescriptions for diabetes mellitus and another patient (D. O.) a gluten-reduced diet because his daughter had coeliac disease.

The mean daily gluten intake varied from 6.2 to 18.5 g daily (Table I). The mean intake of the group (10.7 g/d) is significantly less than in a reference group of 34 patients with dapsone-requiring DH on non-restricted diet ( $p < 0.05$ , Student's *t*-test) (7).

Patients in remission consume less ascorbic acid and dietary fibre (Table II) than DH patients with normal diet on dapsone (21). This could be referred to a low intake of fruit, vegetables and cereals.

#### *Iodine excretion*

Five patients had previously been instructed to restrict their dietary iodine intake, by replacing the ordinary iodine-enriched salt with a low-iodine salt, and to avoid salt-water fish and shellfish. Their mean daily iodine excretion was 1.07  $\mu\text{mol}$ , contrasting with 1.49  $\mu\text{mol}$  for the remaining two patients (nos. 1 and 7).

## DISCUSSION

It is noteworthy that the highest rate of spontaneous remission of DH so far was found in Sweden (5). Possible explanations are genetic and environmental differences, the completeness of patient collection and the attitude towards recommendation of a gluten-free diet. In fact the present figure of 29% may be an underestimate since cases in long-standing remission may be unknown. It should be noted that the onset of disease in our patients varied from childhood to old age. However, they all had mild symptoms from onset, supporting the finding of Fry et al. (2). The clinical spectrum of DH is evidently broader than generally considered. It is apparent that a diagnosis of DH should also be considered in cases with a discrete eruption and minor itching, and we therefore suggest liberal use of skin biopsies for direct immunofluorescence examinations (11).

The skin IgA remained in all patients, which is in accordance with the findings of Fry et al. in 5 patients in natural remission (2). The role of these deposits in the blister pathogenesis has been questioned, partly owing to their persistence during successful dapsone treatment and long after the rash has cleared on GFD (3). The persistence of IgA also during spontaneous remission is a further indication that additional factors might be responsible for the development of skin lesions.

Our patients in remission did not differ from symptomatic DH patients concerning the

Table II. Mean daily nutrient intake in eight patients with dermatitis herpetiformis in spontaneous remission

	All patients	Range	Males (4)	Females (4)
Gluten, g/day	10.8	6.2-18.5	11.9	9.7
Energy, MJ/day	11.5	8.6-14.9	13.7	9.3
Protein, g/day	91	75-123	104	78
Fat, g/day	121	69-168	153	90
Carbohydrate, g/day	292	242-380	329	256
Ascorbic acid, mg/day	66	36-172	74	59
Iron, mg/day	19	15-24	20	18
Fibre, g/day	7	2-11	8	6

frequency of HLA-B8, achlorhydria or small-bowel enteropathy (3, 18). In fact, five of the eight patients had proven or probable enteropathy at the time of this study, although the severity is unknown owing to lack of morphological data. Interestingly, the patient with the highest gluten intake (18.5 g/day) had subtotal villous atrophy and had noticed loose stools for the last few months and yet had no skin symptoms. The presence of villous atrophy but no skin rash in DH patients has previously been reported in a few patients after successful GFD (2).

Our earlier finding of a dose-response relationship between estimated dietary intake of gluten and intestinal reaction with villous atrophy restricted to patients with a daily gluten intake exceeding 12 g (7) led us to study if a clinical remission could be due to a low intake of gluten. The intake as evaluated from current food habits was below 12 g/d in six out of eight patients, suggesting that low gluten intake could contribute to the remission at least in some patients. As the diet of these patients in remission still contained considerable amounts of gluten, varying gluten sensitivity in the small intestine and the skin could be suspected, as suggested by e.g. Fry et al. (2).

The link between the skin and gut in DH is still obscure. An immunological messenger, e.g. circulating immune complexes or various antibodies, has been suggested (3). However, the occurrence of gliadin antibodies in symptomless persons casts further doubts on their presumed pathogenetic role in the occurrence of skin lesions. Another explanation could be that a "leaky gut", damaged by gluten, allows the absorption of compounds able to initiate the basal membrane zone reactions (9). The urinary iodine excretion was low due to voluntary dietary restriction of iodine in the remitting patients. Iodine excretion is widely accepted as a satisfactory index of iodine intake (22). The result is therefore compatible with the hypothesis that dietary iodine might influence the mechanism inducing skin lesions. Further studies are required for clarification. In addition, a long-term daily intake below the minimum daily iodine requirement carries a risk of goitre development and hypothyroidism (23). There is also an increased incidence of thyroid diseases in DH, usually attributed to a predisposition to autoimmune reactions (24). The consequences of a low-iodine diet in DH for thyroid morbidity and the severity of the skin lesions merit further studies.

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