Dermatitis herpetiformis: a comparative assessment of skin and bowel abnormality

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SUMMARY We reviewed 18 patients with a clinical diagnosis of dermatitis herpetiformis who were being treated with dapsone and were on an unrestricted diet. Diagnosis was confirmed by finding IgA deposits in the dermal papillae of unaffected skin. Dapsone was discontinued and biopsy of affected skin was carried out when the typical rash reappeared. The biopsy findings were graded according to the severity of the histological changes. Small bowel tissue from each patient was examined and graded by stereo- and routine microscopy. Thirteen specimens (72%) were stereo-microscopically abnormal; all 18 showed villous atrophy, either partial or subtotal; and in 13 (72%) the interepithelial lymphocyte count was increased. No correlation was found between the histological severity of the skin and the small bowel lesions. Seemingly the severity of the skin rash in dermatitis herpetiformis is no guide to the degree of small bowel abnormality.

The occurrence of gluten-sensitive enteropathy in patients with dermatitis herpetiformis (DH) has been well established (Fry *et al.*, 1967; Fry *et al.*, 1968; Shuster *et al.*, 1968; Fry *et al.*, 1969; Fry *et al.*, 1972). The incidence of small bowel mucosal lesions, however, varies widely in different series, ranging from 25% (Ruppin *et al.*, 1975) to 81% (Scott *et al.*, 1976), and to almost 100% (Fry *et al.*, 1974). A patchy distribution has been suggested as a partial explanation of this variation in incidence (Brow *et al.*, 1971; Scott and Losowsky, 1975). It has also been proposed (Fry *et al.*, 1972; Stevens *et al.*, 1975) that in some patients with DH the mucosal abnormality may be detected only by more sensitive techniques such as intestinal enzyme assay and interepithelial lymphocyte counting, and Fry *et al.* (1972; 1974) have used the increased interepithelial lymphocyte count as an index of mucosal abnormality.

In studying the skin lesions of DH Piérard and Whimster (1961) laid down criteria which they considered characteristic of the disorder. Subsequent studies (Lever, 1965; Connor *et al.*, 1972) suggested that these criteria, although characteristic of DH, were not in fact pathognomonic. Recent studies (Fry and Seah, 1974; Seah and Fry, 1975) propose that the finding of IgA in the dermal papillae of unaffected skin is the simplest and most reliable way of establishing the diagnosis.

In the light of these developments we reviewed 18

clinically diagnosed, dapsone-treated patients with DH. Having confirmed the diagnosis by finding IgA in the dermal papillae of unaffected skin in all patients we withdrew dapsone and examined by biopsy both the affected skin (on the reappearance of the rash) and the small bowel in each patient. The purpose of the study was to see whether there was a correlation between the severity of the lesions in the skin and in the small bowel mucosa.

Patients and methods

Eighteen patients (11 men, 7 women) aged from 17 to 73 years were studied. Their DH had initially been diagnosed on the appearance, site, and pruritic nature of the rash together with its response to dapsone. They had been treated for periods varying from three months to 16 years and all were on a normal diet.

The period between withdrawal of dapsone and the appearance of the rash varied from four days to eight weeks. Tissue from maculopapular or vesicular skin lesions was taken for biopsy under local anaesthesia from the elbow region and processed for routine microscopy. Punch (4 mm) biopsy specimens of unaffected skin were taken under local anaesthesia from the extensor surface of the forearm distal to the elbow and at least 2 cm from the site of biopsy of affected skin. These specimens were snap frozen and examined by direct immunofluorescence using monospecific fluorescein isothiocyanate (FITC) conjugated anti-human IgG, IgM, and IgA.

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The histological features of the biopsies of affected skin were assessed according to the criteria of Piérard and Whimster (1961). The severity of the lesion in each case was graded according to the number of specific criteria present. Twelve criteria were used (Table 1).

Specimens for small bowel biopsy were taken from the proximal jejunum using a Crosby capsule or, when this was unsatisfactory, from the second or third part of the duodenum by direct vision using a side-viewing duodenoscope (JFB 2). The specimens were examined stereomicroscopically and graded into one of four categories: flat, convoluted, leaves only, and leaves and fingers. The specimens were then fixed in formol saline for routine processing and 5 μ sections were stained with haematoxylin and eosin. The histological appearances were graded as normal, partial villous atrophy (mild, moderate, and severe), and flat (subtotal villous atrophy). Interepithelial lymphocyte counts were carried out on each specimen. In villous and convoluted specimens counts were made on the cells at the sides and tips of the villi and in flat specimens on the surface cells. Five hundred epithelial cells were counted in each specimen and the results were expressed as lymphocytes per 1000 epithelial cells. For the purpose of this study we accepted as abnormal counts of over 200 lymphocytes per 1000 epithelial cells (Fry *et al.*, 1974). Further reference will be made to this point in the discussion.

Results

The number of histological criteria fulfilled in assessing the biopsies of affected skin is shown in Table 2. In nine patients (50%) not more than eight criteria were fulfilled. Only two patients (11%) fulfilled all 12 criteria. Fibrillary or microgranular IgA

Table 2 Histological assessment of biopsies of small bowel and affected skin in 18 patients with dermatitis herpetiformis

Case no.	Stereomicroscopy	Routine microscopy	Interepithelial lymphocytes*	No. of criteria fulfilled†
1	Leaves	PVA, moderate	205	3
2	Convoluted	PVA, severe	400	5
3	Flat	Flat	296	8
4	Flat	Flat	327	10
5	Leaves and fingers	PVA, mild	155	10
6	Leaves and fingers	PVA, severe	420	10
7	Convoluted	PVA, severe	184	11
8	Convoluted	PVA, severe	397	12
9	Convoluted	PVA, severe	263	1
10	Flat	Flat	390	4
11	Convoluted	PVA, moderate	240	10
12	Flat	Flat	180	12
13	Convoluted	PVA, moderate	265	8
14	Convoluted	PVA, moderate	137	11
15	Convoluted	PVA, severe	316	10
16	Convoluted	PVA, severe	328	7
17	Leaves	PVA, moderate	247	4
18	Leaves	PVA, mild	180	4

PVA = partial villous atrophy.

*Interepithelial lymphocytes/1000 epithelial cells.

†Maximum no. possible = 12.

deposits, however, were detected in the papillary dermis of unaffected skin in all patients.

The appearance of the small bowel biopsies is also listed in Table 2. The stereomicroscopic appearance was abnormal in 13 cases (72%): four were flat and nine convoluted. Five specimens (28%) were stereomicroscopically normal: three showed leaves and two leaves and fingers. Routine histology showed all 18 specimens to be abnormal: four (22%) were flat and 14 (78%) showed partial villous atrophy of varying degree. The interepithelial lymphocyte count was raised in 13 cases (72%): in seven (38%) it was greater than 300 per 1000 epithelial cells; in six (33%) between 200 and 300; and in five (28%) below 200. Comparison of the relative severity of skin and bowel lesions in each patient failed to show any correlation (Figs 1-3).

Discussion

The patients studied were originally diagnosed on the clinical appearance, distribution and pruritic nature of the rash, and the response to dapsone. Fry and Seah (1974) and Seah and Fry (1975) thought that the finding of IgA in the dermal papillae of the unaffected skin was the most specific diagnostic criterion of DH. We have taken this finding to be highly suggestive of DH. All our patients had this abnormality, whereas the histological changes on routine microscopy showed a wide variation. As with the study of Fry and Seah (1974), histological examination of

Table 1 Skin biopsy criteria in dermatitis herpetiformis (Piérard and Whimster, 1961)

Site	Specific features
Papillary dermis	Oedema of papillae Papillary microabscesses Connective tissue necrosis
Floor of lesion	Papillary outlines Polymorphs and eosinophils Pyknotic nuclei and cellular debris
Fluid within blister	Fibrin threads Polymorphs and eosinophils Shadow epidermal cells
Roof of lesion	Stretching of epidermis Progressive necrosis of lower epidermal layers Epidermis cleanly detached

Fig. 1 Graphical representation of skin criteria fulfilled (▲) when compared with stereomicroscopic appearance of bowel (Δ) in each patient. No correlation seen.

Fig. 2 Graphical representation of skin criteria fulfilled (▲) when compared with routine microscopic appearance of bowel (X) in each patient. No correlation seen.

affected skin was altogether unhelpful in establishing a diagnosis in six patients (33%) whose biopsies showed five or fewer of the requisite criteria. The criteria of Piérard and Whimster (1961), although characteristic, are not pathognomonic of DH. Nevertheless, they remain a useful basis on which to grade the severity of skin lesions in this disorder. The finding of IgA in the dermal papillae of unaffected skin, if shown conclusively to be specific for DH,

would be a valuable diagnostic tool.

All our patients had evidence of enteropathy. Histological abnormalities were noted in all (Table 2); 13 (72%) were abnormal on stereomicroscopy; and interepithelial lymphocyte counts were raised in 13 (72%). There was reasonably good correlation between the degree of villous atrophy on the one hand and both the stereomicroscopic appearance and the interepithelial lymphocyte count on the other. The

Fig. 3 Graphical representation of skin criteria fulfilled (▲) when compared with interepithelial lymphocyte count (○) in each patient. No correlation seen.

consistently abnormal small bowel histology in the present series contrasts with the findings of Scott *et al.* (1976), who reported 23% of patients in whom biopsy was normal on both stereomicroscopy and routine histology. This discrepancy may be partly explained by the apparently higher incidence of coeliac disease in Ireland (Mylotte *et al.*, 1973). Equally it may be argued that our cases 2 and 18 (Table 2) with normal stereomicroscopic appearances, normal interepithelial lymphocyte counts, and only mild partial villous atrophy are in fact variations of normal. We think, however, bearing in mind the patchy distribution of the small bowel lesions in DH (Brow *et al.*, 1971; Scott and Losowsky, 1975), that the finding of even a mild degree of villous atrophy in a *single* biopsy in these patients is significant. The incidence of mucosal abnormality in our series accords best with that of Fry *et al.* (1974).

The exact definition of a raised interepithelial lymphocyte count and the precise significance of such a finding remain to be fully elucidated. Several studies have proposed a normal range for interepithelial lymphocytes, but these normals vary per 1000 epithelial cells from 69-285 (Fry *et al.*, 1974), 80-270 (Mavromichalis *et al.*, 1976), 60-400 (Ferguson and Murray, 1971), to 74-428 (Scott *et al.*, 1976), and 132-450 (Stevens *et al.*, 1975). We have applied the range of Fry *et al.* (1974) (69-285), in which all but four of their controls had counts of under 200, since this accorded best with the stereo- and routine

microscopic findings in our patients. The non-specificity of a raised interepithelial lymphocyte count as shown by Mavromichalis *et al.* (1976) indicates the need for correlating the count with both the microscopic appearance of the mucosa and the response to gluten withdrawal and challenge if a diagnosis of coeliac disease is to be made. We have also noted that several biopsies showing morphologically abnormal villi had normal interepithelial lymphocyte counts, although Mavromichalis *et al.* (1976) found this phenomenon only in enteropathies other than coeliac disease. The range of interepithelial lymphocytes in our patients (137-420) is considerably lower than that reported in abnormals in similar series. The reason for this is not clear.

The purpose of this study was to see whether there is a correlation between the severity of the skin lesions and those of the small bowel in DH. Evidently (Figs. 1-3) there is no such correlation. Thus in all patients with DH biopsy of the small bowel should be done to ascertain the degree of mucosal abnormality irrespective of the state of the skin. Diagnosis of villous atrophy in these patients merits treatment with a gluten free diet both to correct the intestinal abnormality (Fry *et al.*, 1968; Marks and Whittle, 1969; Weinstein *et al.*, 1970) and to minimise the dose of drugs necessary to control the skin lesions (Heading *et al.*, 1976). A gluten free diet may not prevent malignant complications in patients with coeliac disease (Holmes *et al.*, 1976). The evidence for this is as yet by no means conclusive, and until it is we think that a gluten free diet for patients with severe coeliac disease remains mandatory simply because it may prevent malignancy.

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