Skin Biopsies in Relatives of Patients with Dermatitis herpetiformis

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Abstract. Out of 109 patients with dermatitis herpetiformis (DH) only one was known to have a first-degree relative with the disease. This is in keeping with previous reports that the familial incidence of DH is low. Study of the family in which two siblings were affected showed both to have HLA-B8 whereas a third, unaffected sibling did not have this antigen. This finding supports the view that both genetic and environmental factors are involved in the pathogenesis of DH. 20 first-degree relatives of 10 other patients with DH had skin biopsies examined by immunofluorescence for the presence of IgA, but none proved positive.

Key words: Dermatitis herpetiformis

Dermatitis Herpetiformis (DH) is a rare disease. It is characterized by an intensely itchy blistering rash distributed typically over the elbows, knees and buttocks. The rash responds well to sulphone drugs, the majority of cases being controlled with 100 mg dapsone daily. By modern criteria, the diagnosis can only be made by direct immunofluorescence which shows the presence of IgA in the dermal papillae of uninvolved skin (1).

Nearly all patients with DH have an associated enteropathy, indistinguishable from coeliac disease CD, though in many cases it is less severe (2). The finding that both the rash and the enteropathy of patients with DH improve with a gluten-free diet indicates that DH, like CD, is gluten dependent (3). In both DH and CD the incidence of the histocompatibility antigen HLA-B8 is over 80%, suggesting that there is a genetic predisposition to both diseases (4). However, whereas in CD there is a recognized family incidence of the disease (5, 6), there are very few reports of DH being present in members of the same family. Marks et al., in reporting a case of DH occurring in monozygotic twins (7), stated that they were only aware of 6 other cases of DH occurring in the same family. Björnberg & Hellgren (8) found that none of 53 DH patients studied had a first-degree relative affected, and Reunala and his colleagues (9) found only two instances of familial DH out of 184 patients studied.

Marks et al. reported that 32% of relatives of patients with DH have non-symptomatic enteropathy (10). More recent studies (11) have shown that an oral gluten load could induce changes of CD in close relatives of patients with CD in whom there had been no previous evidence of enteropathy. These changes could not be induced in normal controls. Both of these observations indicate that sub-clinical manifestations of gluten sensitivity may be present in relatives of affected patients. The diagnostic marker for DH is the presence of IgA in uninvolved skin—it is not found in the skin of patients with CD (12). The IgA persists in the skin of DH patients even in the rare instances of spontaneous remission (3), suggesting that IgA might also be found in individuals with a predisposition for the disease, i.e. with sub-clinical DH.

This study investigates the possibility that IgA is present in the skin of relatives of patients with DH. It also reports the incidence of overt DH in the relatives of 109 patients with DH who have been seen at St. Mary's Hospital, London, since 1969, and the results of HLA typing in one family in whom 2 out of 3 siblings had DH.

PATIENTS AND METHODS

20 first-degree relatives of 10 patients with DH were studied. None had any symptoms suggestive of either DH or CD. There were 9 male and 11 female relatives of average age 32.4 years (range 16-69). 4-mm punch biopsies of forearm skin were taken under local anaesthesia, embedded in OCT medium (Lab Tek Inc.) and snap frozen in liquid nitrogen. They were stored at −70°C until processing. 4-μm cryostat sections were then studied for the presence of IgA, IgG, IgM and C3 by direct immunofluorescence, as described previously (13). In addition, all relatives had venous blood taken for detection of antigliadin antibodies (AGA) by both indirect immunofluorescence and the enzyme-linked immunosorbent assay (ELISA) as described previously (15).

Of the 109 patients with DH who have been seen at St. Mary's Hospital, London, since 1969 (in all of whom the diagnosis has been established by immunofluorescence criteria), only one has had a first-degree relative with

DH. The family members studied in this case were as follows: the father (aged 68) and mother (aged 65) of the propositus, neither of whom had the disease clinically, the propositus (a male aged 33 who developed DH at the age of 32, his sister (aged 26 who developed DH at the age of 16) and an unaffected brother aged 28 at the time of the study. The parents were not consanguineous. All members of the family had clinically normal skin sampled for the presence of immunoglobulins and blood for the presence of AGA and for HLA typing for A and B loci. The HLA typing was performed by the NIH microcytotoxicity test (14). The two affected siblings had had small intestinal biopsies taken from the duodenal–jejunal flexure prior to commencing a gluten-free diet. The macroscopic appearance was assessed as previously described (2).

RESULTS

None of the 20 relatives studied had IgA in their skin or AGA in the serum. In the family with two siblings with DH, both affected members had IgA deposits in the papillary dermis of uninvolved skin. No other immunoglobulin and no C3 was found. Both affected members had AGA of IgA class and both had macroscopically abnormal small intestine biopsies—convoluted in the case of the propositus and flat in the case of his sister. Neither parent, nor the unaffected sibling had immunoglobulins or C3 in the skin biopsy or AGA in the serum. The results of HLA typing are given in Fig. 1.

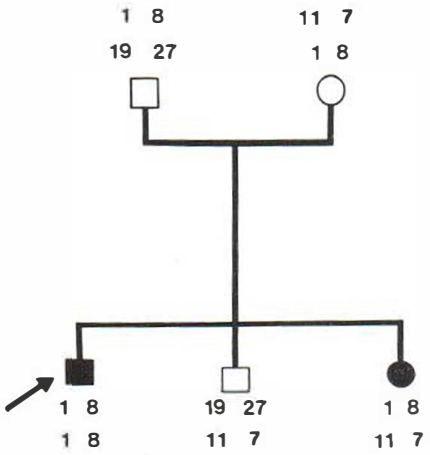

Fig. 1. HLA typing in family with two affected members.

DISCUSSION

None of the 20 clinically normal relatives of the 10 patients with DH had IgA deposits in their skin—a finding similar to that of Reunala and his colleagues (9). If it is accepted that the presence of IgA in the skin is a reasonable guide to sub-clinical DH, then there is no evidence of this occurring in relatives of DH patients. None of the patients' relatives had AGA in the serum. We have previously shown that AGA are generally found only in patients with DH who have a severe enteropathy (15). Hence, this finding is not entirely consistent with that of Marks et al. (10), since the majority of the relatives who had enteropathy in their series had convoluted mucosae and in one instance it was flat.

The findings of this study are consistent with the previous reports of a low family incidence of DH (7, 8, 9). The family reported here, with two siblings affected, was the only case of first-degree relatives having DH out of 109 patients studied. All 3 siblings of the family had the same environmental background yet only 2 have developed DH. However, both the affected siblings had HLA-B8, whereas the unaffected sibling did not. This finding suggests that DH is caused by a combination of both genetic and environmental factors. However, the problem remains as to why there is such a low family incidence of DH compared with CD. It may be that the two diseases are coded for by different genes with differing penetrance, rather than being different manifestations of the same gene.

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HLA Studies in Chronic Dermatophytosis Caused by *Trichophyton rubrum*

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Abstract. The HLA-ABC antigens were investigated in 34 and DR antigens in 28 patients with chronic dermatophytosis caused by *Trichophyton rubrum*. The distribution of the antigens did not differ from that of the controls. Abnormal immune response may be of importance in the susceptibility to chronic dermatophytosis, but HLA-controlled immune mechanisms seem unlikely.

Dermatophytosis due to *Trichophyton rubrum* is a common skin disorder and usually of minor importance. In some cases, however, the disease is resistant to treatment and spreads from the usual location in the lateral toe clefts to involve the foot soles, the palms and/or a varying number of finger and toe nails. The clinical response to the invasion of the dermatophyte in such cases is non-inflammatory, showing slight erythema but pronounced desquamation and keratinization, followed by fissuring. The nails display subungual keratosis, onycholysis, brittleness and discolouration.

This pathological picture is found mainly in males and has been observed to occur in several members of a family. A genetic disorder might therefore be a factor in the development of the symptoms. The lack of response to treatment might indicate a possible immunological disorder. Chronic dermatophytosis (CD) is occasionally associated with atopy (1, 2) and specific IgE to *T. rubrum* has been demonstrated in these patients (4). To investigate the possibility that CD may have a genetic and possibly an immunological background, we found it worthwhile to study the HLA antigens in this disorder, since the HLA system is involved in a variety of immune responses. To our knowledge, such studies have not been reported previously.

PATIENTS

The study involved 34 patients with CD of hands, feet and nails persisting for 3–45 years (mean 16.7 years). All had undergone long periods of medication with griseofulvin and 26 of them also with Ketoconazole, with varying clinical response but without mycological cure in any case.

METHODS

Tissue typing was performed by using the NIH technique for the HLA-ABC antigens and with the 7th workshop technique for the DR antigens, as described elsewhere (3). Lymphocytes from the patients were typed with antisera defining 11 HLA-A, 20 HLA-B, 5 HLA-C and the following HLA-DR antigens: DR 1, 2, 3, 4, 5, 7, w8 and 9 (we do not consider DRw6 sufficiently well defined). All patients were typed for ABC, while only 28 were typed for HLA-DR. The control groups included 426–3301