

Difference in Ceramide Composition between "Dry" and "Normal" Skin in Patients with Atopic Dermatitis

Sir,

Many patients with atopic dermatitis have widespread dry skin, which has a disturbed water barrier function (1). Stratum corneum lipids play an important role here. Recently, various authors have reported that dry skin in people with atopic dermatitis shows a marked reduction in ceramides (2, 3). We measured the ceramides in dry and normal skin of patients with atopic dermatitis and compared the results with those for normal individuals.

MATERIALS AND METHODS

A total of 44 patients (15 males and 29 females) with mild atopic dermatitis were included in this study. They ranged in age from 15 to 31 years. All patients fulfilled the diagnostic criteria of Hanifin & Rajka (4). In 14 patients, the volar surface of the forearm showed dry and rough skin that exhibited white dermographism. In 30 patients, the flexor forearm showed normal-appearing smooth skin that revealed red dermographism. Patients with ichthyosis vulgaris were excluded. No preparations were applied to the forearm for 4 weeks preceding the investigation. All the measurements were made on the flexor surface of the mid forearm. Twenty-five age-matched healthy subjects were included as controls. The study details were discussed in full with each subject and informed consent for participation was obtained.

Previous studies (5, 6) have demonstrated that red dermographism commonly occurs in areas of normal-appearing skin of patients with atopic dermatitis, whilst white dermographism consistently occurs in areas of dry skin in these patients. In the present study, therefore, dry skin was defined as a rough, finely scaling, non-inflamed surface that showed white dermographism. Normal skin was defined as a smooth, clear skin that showed red dermographism.

Skin surface lipids were collected from the flexor mid forearm using the cup method (7).

The lipid extracts were weighed and determination of lipid classes was accomplished using thin-layer chromatography separation. The thin-layer chromatograms were developed twice with chloroform/methanol/acetic acid (190:9:1 by volume) for separation of six ceramide fractions (2).

Data were expressed as mean \pm SD. Student's *t*-test was employed for statistical analysis. A *p* value of 0.05 was accepted as statistically significant.

RESULTS

The weight of all sebaceous lipids (squalene, wax esters, triglycerides and free fatty acids) in the dry skin of patients with atopic dermatitis did not differ from those in normal individuals. The weight of total ceramides and of phospholipids in the atopic dry skin were lower than those in normal individuals ($p < 0.05$, $p < 0.05$, respectively). The weight of other stratum corneum lipids (cholesterol esters, cholesterol and cholesterol sulfate) did not differ from those in normal individuals.

The weights of all sebaceous lipids in the normal-appearing skin of patients with atopic dermatitis were similar to those in normal individuals. The weights of all stratum corneum lipids in the normal-appearing skin of atopic patients did not differ from those in normal individuals.

The weight of ceramide 1 in dry skin of patients with atopic dermatitis was significantly lower than that in normal individuals, whereas the weights of other ceramides were similar to

Table I. Mean weight ($\mu\text{g}/\text{cm}^2$) of ceramide fractions in dry and normal skin of patients with atopic dermatitis (mean \pm SD)

| Ceramide fraction | Patients with atopic dermatitis | | Normal individuals |
|-------------------|---------------------------------|-----------------|--------------------|
| | Dry skin | Normal skin | |
| Ceramide 1 | 0.57 \pm 0.26* | 1.10 \pm 0.66 | 1.20 \pm 0.48 |
| Ceramide 2 | 1.54 \pm 0.99 | 2.06 \pm 1.31 | 2.04 \pm 0.73 |
| Ceramide 3 | 0.75 \pm 0.43 | 0.92 \pm 0.58 | 1.10 \pm 0.58 |
| Ceramide 4 + 5 | 1.90 \pm 1.11 | 2.74 \pm 1.33 | 2.89 \pm 1.17 |
| Ceramide 6 | 2.10 \pm 1.06 | 2.44 \pm 1.16 | 2.73 \pm 1.15 |

* $p < 0.05$ (compared with normal individuals).

those in normal individuals (Table I). No difference in the value of each ceramide fraction was found between normal skin in the atopic patients and the skin of normal individuals.

DISCUSSION

The present study demonstrated that sebaceous lipids were not decreased in the dry skin of patients with atopic dermatitis. This is in accordance with previously reported data (3).

An interesting finding of the present study was that both the total ceramides and ceramide 1 were not decreased in the normal-appearing skin of patients with atopic dermatitis. These findings suggest that the biosynthesis of ceramides is not disturbed in an uninvolved skin of atopic patients. Some previous studies (2, 3) reported a decrease in ceramides in the normal-appearing skin of patients with atopic dermatitis. The reason for the difference between our study and these other studies is unclear. One possibility may be a difference in the selection of patients. In the present study, we selected patients with only mild atopic dermatitis, because it was often difficult to find normal skin in patients with widespread dermatitis. In previous studies (2, 3), however, there was no description of the degree of dermatitis in the patients examined. Secondly, the definition of normal skin might be different. We selected normal-appearing skin that showed red dermographism. But it was not clear whether the normal skin in the previous studies (2, 3) showed red or white dermographism.

The present study further confirmed the findings of previous works (2, 3), that the dry skin of patients with atopic dermatitis shows a decrease in total ceramides and ceramide 1. Various authors (2, 8, 9) assume that the total skin of these patients inherently shows deranged biosynthesis of ceramides and that this is an aetiological factor in atopic dry skin. However, this assumption is unlikely, because ceramides are not decreased in areas of normal-appearing skin of patients with this dermatosis. Another possibility is that the deficient biosynthesis of ceramides in areas of dry skin of atopic dermatitis is secondary to the deranged keratinization due to a mild ongoing dermatitis.

REFERENCES

1. Loden M, Olsson H, Axell T, Linde YW. Friction, capacitance and transepidermal water loss (TEWL) in dry atopic and normal skin. *Br J Dermatol* 1992; 126: 137–141.

2. Imokawa G, Abe A, Jin K, Higaki Y, Kawashima M, Hidano A. Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? *J Invest Dermatol* 1991; 96: 523–526.
3. Di Nardo A, Wertz P, Gianetti A, Seidenari S. Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. *Acta Derm Venereol (Stockh)* 1998; 78: 27–30.
4. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980; Suppl 92: 44–47.
5. Uehara M, Ofuji S. Abnormal vascular reactions in atopic dermatitis. *Arch Dermatol* 1977; 113: 627–629.
6. Wong SS, Edwards C, Marks R. A study of white dermographism in atopic dermatitis. *J Dermatol Sci* 1996; 11: 148–153.
7. Serizawa S, Osawa K, Togashi K, Yamamoto A, Ito M, Hamanaka S, Otsuka F. Relationship between cholesterol sulfate and intercellular cohesion of the stratum corneum: demonstration using a push-pull meter and an improved high-performance thin-layer chromatographic separation system of all major stratum corneum lipids. *J Invest Dermatol* 1992; 99: 232–236.
8. Melnik BC. Disturbance of epidermal lipid metabolism and barrier function in atopic eczema. In: Ruzicka T, Ring J, Przybilla B, ed. *Handbook of atopic eczema*. Berlin: Springer Verlag, 1991: 296–305.
9. Murata Y, Ogata J, Higaki Y, Kawashima M, Yada Y, Higuchi K, et al. Abnormal expression of sphingomyelin acylase in atopic dermatitis: an etiologic factor for ceramide deficiency? *J Invest Dermatol* 1996; 106: 1242–1249.

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Clinical and Virological Comparison of 3 Patients with Erythema Multiforme

Sir,

Erythema multiforme (EM) is a polymorphous self-limited, often recurrent eruption that can follow drug administration or infection with various agents including herpes simplex virus (HSV). HSV-associated EM (HAEM) is presently distinguished from other EM eruptions based on clinical severity or the presence of target lesions and oral mucosa involvement. Here we describe 3 patients whose management was complicated by adherence to sole clinical criteria.

CASE REPORTS

Patient 1

Patient 1 is a 28-year-old Caucasian man seen in July 1992 a few days after onset of recurrent HSV labialis with symmetrical target lesions on the hands, feet, knees and penis but no oral mucosa involvement. He was placed on a 5-day course of 40 mg prednisone/day and acyclovir 1 g daily for a week before reducing the latter drug to a maintenance dosage of 600 mg. With this treatment, the patient had no recurrent eruptions until March 1994 when he presented 5 days after an EM eruption that followed a HSV episode. Biopsy of the EM lesion on his lateral left palm showed ulcerated and focally necrotic epidermis with dyskeratotic keratinocytes adjacent to the ulcer. The underlying upper epidermis contained a band-like lymphohistiocytic infiltrate. The patient's HSV recurrences were suppressed for the next year on an oral dose of acyclovir of 400 mg daily. In June 1995 he discontinued the medication and promptly developed a recurrent HSV episode that was not accompanied by EM. Three additional episodes of recurrent HSV ensued within the next 3 months, during which the patient developed target lesions on the wrists, but was free of mucosal involvement.

Patient 2

Patient 2 is a 44-year-old Caucasian woman who had 1 episode of HSV labialis in 1989. She noticed an erythematous lesion of grouped vesicles on her hip in August 1991. Within a few days small target lesions

appeared on her lower legs but they spontaneously remitted within a week. One year later, in August 1992 the hip and leg lesions recurred. A Tzanck smear of the hip lesion was positive for multinucleated cells. The patient was placed on oral acyclovir at divided doses ranging from 1.2 to 1.6 g/day, but in spite of therapy, leg and arm lesions appeared 4 or 5 times over the next 5 years. They were not associated with a clinical recurrence of the HSV lesions, exposure to the sun, intercurrent disease, medication or reduction in the dose of daily acyclovir. Mucosal lesions were not seen. In late October 1997 the patient noticed several erythematous papules and plaques ranging from 2 to 4 mm in diameter over the lower arms and legs which were not accompanied by hip vesicles. No vesiculation was present, but the wrist lesion was crusted slightly in the centre. Target lesions were not seen. Biopsies of 2 lesions on the right dorsal wrist and hand showed an interface lichenoid lymphohistiocytic infiltration. A subepidermal bulla was seen in the 1992 specimen, but epidermal necrosis was a feature of both 1997 specimens. Significant apoptosis was present in all lesions.

Patient 3

Patient 3 is a 44-year-old Caucasian woman with a history of recurrent HSV located in the centre of her lower lip confirmed by virus isolation. At the end of September 1996 she noticed a lip lesion 4 days after ingesting naproxen for menstrual pain. It was at a different site from her HSV recurrences and was followed by a limited number of erythematous macules on her upper chest and distal hands. The following month the patient presented with a 2 mm diameter unilocular tense vesicle on the right lip commissure. An aspirate obtained within 24 h of onset was negative for virus isolation. Within 36 h, the patient developed a classical HAEM picture, with ulcerative blood crusted lesions which covered the mucosae of the entire lower and central lip and scattered areas of the upper lip. Multiple target lesions appeared rapidly on her upper chest, arms and hands. An active lesion above the left elbow was biopsied and the patient was begun on 30 mg prednisone daily. After 4 days, acyclovir (1 g/day) was added for an additional week because of poor clinical response. In late October and November, the patient had additional episodes of target eruptions, each progressively