Substance P Is Not Involved in Primary and Secondary Erythromalgia

Sir,

Erythromalgia is a syndrome of bilateral symmetric burning and redness of, mainly, the lower extremities. Symptoms can be initiated by exercise or exposure to heat, while rest and cold bring relief (1). Primary erythromalgia usually arises in childhood as an invariable variant of painful red extremities in the absence of thrombocytopenia or any other underlying disorder (2). Secondary erythromalgia usually develops at adult age in association with or without an apparent underlying disorder. In some cases treatment of the underlying disorder is difficult and therefore symptoms may persist throughout life (3). Secondary erythromalgia can arise as a side-effect of drugs. In those cases relief can be obtained by withdrawal of the causative drug. The pathogenesis of primary and secondary erythromalgia remains to be elucidated. A neurogenic aetiology or vasomotoric dysregulation has been suggested as a potential cause of erythromalgia.

Vasoactive neuropeptides, such as substance P (SP), are released from peripheral terminals from sensory nerve endings in human skin and are involved in (neurogenic) inflammatory cutaneous reactions (4). SP, when injected intradermally, elicits a triple response with local erythema, a rapidly spreading flare and a slowly developing wheal (5). The fact that erythromalgic attacks are precipitated by an increase in skin temperature has given rise to speculations that temperature triggers release of inflammatory and pain mediating substances in sensitive areas of predisposed patients (6). In this respect SP might have a role in the pathogenesis of erythromalgia. Further, hope is fuelled by the fact that symptoms of secondary erythromalgia in one patient responded to topical application of capsaicin cream (7). Repeated application of capsaicin depletes the sensory neurons of SP and suppresses the flare response to SP (8). Consequently, we investigated the immunoreactivity of SP in fluid from artificial blisters from healthy and pathological skin in patients with primary and secondary erythromalgia.

PATIENTS AND METHODS

Patients
Six women and one man (age 28–76 years), suffering from erythromalgia, were invited to take part in the study. A 28-year-old patient suffered from primary erythromalgia and 6 had secondary erythromalgia. The associated conditions were autoimmune disease of undetermined significance (1); hypertension (1); Sjögren's syndrome (2); unknown (2). Prior to the procedure all patients provided their symptoms by putting their feet in warm water or by strenuous exercise.

Artificial blisters
Sucrose blisters were induced on the volar aspect of the erythromalgic foot of every patient (9). Control blisters were evoked on apparent healthy skin on the upper legs. The blister devices were connected to the central suction unit of the hospital, and after application the pressure within the cup was slowly increased to 200 mmHg below the atmospheric pressure. Blisters of 5–10 mm developed 3–4 h after suction. Blister fluid was collected by aspiration with a thin needle and syringe. Samples were immediately frozen to −70 °C.

Radioimmunoassay for SP
The concentration of SP was determined by a commercially available radioimmunoassay (Eurodiagnostica AB, Malmö, Sweden).

Polyclonal antibody against synthetic SP was raised in rabbit. Synthetic SP was radiolabelled with 125I, and SP in blister fluid was measured in duplicate by nonequilibrium radioimmunoassay (10). For measurement of SP, 100 µl blister fluid was used. The lower detection limit of this method is 10 pg/ml (7 pmol/l). The study protocol was approved by the Medical Ethical Committee of the University Hospital Dijkzigt in Rotterdam, The Netherlands. Written informed consent was obtained from all patients.

RESULTS
The SP concentration in blister fluid extracted from healthy skin in primary erythromalgia was 316 pg/ml and <10 pg/ml in erythromalgic skin. In one patient with secondary erythromalgia the SP content in blister fluid from both erythromalgic and healthy skin was elevated to 111 pg/ml and 120 pg/ml, respectively. In all other patients with secondary erythromalgia the SP concentration in the samples was below the limit of detection.

DISCUSSION
The low concentration of SP in the blister fluid might suggest that SP present in sensory nerve endings in the skin does not diffuse in measurable amounts into the blister fluid. Other investigators using a similar design with a similar sensitive radioimmunoassay have detected increased SP in suction-induced blisters in lesional and control skin of patients with bullous pemphigoid and urticaria (10, 11). Our suction time of 3–4 h was considerably longer than that used in this study (75–90 min), which suggests that inadequate diffusion of cutaneous SP into blister fluid does not explain the low concentrations. On the other hand, it is also possible that a suction time of 3–4 h is too long, allowing proteolytic enzymes to degrade SP. We provoked blisters on the volar aspect of the forefoot, since it was known that the SP concentration is the highest in fingers and toes, opposed to axilla and thigh (12).

It also remains possible that SP is of minor importance as an inflammatory mediator in the pathogenesis of erythromalgia. The concept of neurogenic inflammation as a cause of erythromalgia nevertheless remains an attractive hypothesis. An increased local production of other vasoactive neuropeptides, such as neurokinin A and calcitonin-G-related-peptide (CGRP), could be responsible for symptoms in erythromalgia. Intradermal injection of CGRP leads to a prolonged increase in cutaneous blood flow and erythema, as seen in erythromalgia. Although SP is chemotactic for human T-lymphocytes, CGRP is more potent (13). We have shown earlier that biopsy specimens from erythromalgic skin are characterized by a mild mononuclear infiltrate, which suggests involvement of these vasoactive molecules (19). The contribution of these peptides to the pathogenesis of erythromalgia thus requires further investigation, and in this respect immunoreactive staining of biopsy specimens might be helpful.

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Localized Crusted Scabies in a Patient with Acquired Immunodeficiency Syndrome

Sir,

Crusted (Norwegian) scabies (CS), is a rare variant of infestation with Sarcopites scabei var. hominis, where the skin lesions are extensive, and the thickened horny layer is riddled with innumerable parasites. This condition was first described in lepers by Daniels & Boeck in 1848 (1).

This rare variant of scabies occurs mainly when the host's immune response is impaired and in patients who have a decreased sensation of itch, resulting in less scratching and less destruction of burrows.

In 1986, CS was reported for the first time in infected patients with human immunodeficiency virus (HIV) (2). Subsequently, some additional cases have been described in the literature (3). One case of localized crusted lesions on the toe has earlier been reported (4). We describe a patient with acquired immunodeficiency syndrome (AIDS), who developed an unusual form of CS, involving exclusively the genital area.

CASE REPORT

In June 1995, a 31-year-old HIV-seropositive intravenous drug-abuser was admitted to hospital because of pneumonia. His CD4 count was 14/µl. He had a 1-month history of a generalized intensely pruritic eruption and had been found to have AIDS 3 years earlier. Physical examination on admission showed erythematous papules and excoriations involving predominantly the abdomen, thighs and buttocks. Burrows were found on the interdigital webs of his hands. A biopsy specimen revealed the presence of a scabies mite. The patient was treated with topical gamma benzene hexachloride lotion 1% for 3 days and improved rapidly.

Two months later, he was admitted again to hospital because of pneumonia. His CD4 count was only 7/µl. He had also a keratotic lesion on the penis, which produced local pain and intense pruritus, and which had appeared 1 month earlier. Physical examination revealed extensive thick and confluent keratotic plaques with some greyish crusted, exclusively on the penis (Fig. 1). Other skin lesions were seen. A biopsy specimen showed multiple curved burrows within the cornified layer, of which some extended into the malpighian stratum. These burrows were occupied by great numbers of adult Sarcoptes scabei, with eggs and larvae. Prominent hyperkeratosis with parakeratosis and a hyperplastic epidermis (psoriasiform) were also observed (Fig. 2). Treatment was started with a 5-day course of topical gamma benzene hexachloride lotion 1% in addition to a 10% salicylic acid ointment. Initially, a significant clinical improvement was noted, but the patient was lost for follow-up.

DISCUSSION

HIV infection is today probably the most common disease triggering CS. However, atypical forms of scabies are often complicating in HIV/AIDS patients and predispose to nosocomial transmission. Scabies should therefore be suspected in any HIV/AIDS patient with itching or non-itching eczematous or keratotic lesions. Besides early diagnosis, prompt treatment and strict control measures are extremely important.

The treatment for CS is as for ordinary scabies, although repeated applications may be required with scabicides, and sometimes the sequential use of several agents. Permethrin cream is the preferred scabicide to begin the therapy. The entire skin should be treated, including under the nails (5).