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Antibodies to the *Borrelia burgdorferi* Flagellum in Patients with Scleroderma, Granuloma Annulare and Porphyria Cutanea Tarda*

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It is generally accepted that cutaneous Lyme borreliosis comprises erythema chronicum migrans, lymphadenosis benigna cutis, and acrodermatitis chronica atrophicans. In recent years the tick-borne spirochete *Borrelia burgdorferi* has been associated with a number of other cutaneous disorders. We therefore investigated sera from 175 patients with localized scleroderma (morphea) ($n=64$), systemic sclerosis ($n=74$), granuloma annulare ($n=16$) and porphyria cutanea tarda ($n=21$) with the new, highly sensitive and specific *Borrelia burgdorferi* flagellum ELISA assay. As controls ($n=297$) served normal healthy volunteers and patients with other skin diseases. It was found that the distribution of individual antibody values and the median antibody levels were identical in controls and in patients with scleroderma, granuloma annulare and porphyria cutanea tarda. These data do not support the hypothesis of an ethiological association between *Borrelia burgdorferi* infection and scleroderma, granuloma annulare or porphyria cutanea tarda. *Key words: Borrelia burgdorferi flagellum ELISA.*

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It is generally accepted that cutaneous Lyme borreliosis comprises erythema chronicum migrans (ECM), lymphadenosis benigna cutis (LABC), and acrodermatitis chronica atrophicans (ACA) (1). In recent years the tick-borne spirochete *Borrelia burgdorferi* has been associated with a number of other cutaneous disorders such as morphea (2–4), eosinophilic fasciitis, lichen sclerosis et atrophicus, granuloma annulare, atrophoderma of Pasini and Pierini, pseudolymphoma (5) and porphyria cutanea tarda (PCT) (with sclerodermatous changes) (6). However, reliable evidence of an association between *B. burgdorferi* infection and these disorders has not previously been presented.

The isolation of *B. burgdorferi* is still a low yield procedure and serological tests must therefore be applied for diagnosis and screening. The currently used serological tests are based on whole-cell antigen preparations (7, 8) and yield an unsatisfactorily low diagnostic specificity and sensitivity and are thus not very suitable for screening purposes. This fact may in part account for the high frequency of seropositivity (40–50%) in some reports on patients with localized scleroderma (2–4), a finding that has been questioned by others (9–11).

To evaluate a possible association between *B. burgdorferi* infection and some of these skin disorders, we investigated a large number of patients with scleroderma, granuloma annulare and porphyria cutanea tarda, by means of a new, highly sensitive and specific serological test for Lyme Borreliosis, the *B. burgdorferi* flagellum ELISA (12, 13).

PATIENTS AND METHODS

Patients

A total of 175 patients were included in the study. Their numbers, sex, diagnosis, mean age and disease duration are shown in Table I. Sixty-nine (93%) of the patients with systemic sclerosis had acrosclerosis and 5 (7%) had diffuse sclerosis. In patients with localized scleroderma (morphea), minor skin lesions were found in 30 patients (47%) and widespread lesions in 34 (53%). Biopsies taken in 24 patients (38%) with localized scleroderma showed in all cases a histopathological picture typical of morphea. In both groups, 20% of the patients were in the early phase of the disease (duration <2 years). In 16 patients with granuloma annulare the lesions were localized mainly to the hands and/or feet. Biopsies taken in 11 patients showed histopathological changes typical of

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Table I. *Clinical data of patients and controls investigated regarding antibodies to the Borrelia burgdorferi flagellum*

Diagnosis	No. pts.	Sex ratio (man/woman)	Mean age (years)	Mean disease duration (years)
Patients				
Systemic sclerosis	74	0.3	52 (13–90)	11 (1–30)
Localized scleroderma	64	0.3	37 (10–79)	7 (1–29)
Granuloma annulare	16	0.4	38 (17–71)	2.8 (0.3–6)
Porphyria cutanea tarda	21	2.0	50 (32–72)	3.5 (1–9)
Controls				
Acrodermatitis chronica atrophicans	30	0.4	56 (17–80)	3.6 (0.3–20)
Dermatological control group	97	0.6	51 (15–91)	
Healthy controls	200	0.9	40 (16–71)	

granuloma annulare. Of the 21 patients with porphyria cutanea tarda (PCT), one had sclerodermoid changes of the trunk.

Control groups

Two control groups (Table I) were included in the study. One consisted of 200 healthy individuals (free from skin disease), the other of 97 dermatological patients with a variety of skin disorders (psoriasis, eczema, connective tissue diseases, urticaria, etc.), without clinical evidence of a *B. burgdorferi* infection.

Serological test

An enzyme-linked immunosorbent assay (ELISA) measuring IgG antibodies against the *B. burgdorferi* flagellum was used (12, 13). The 95% specific diagnostic cut-off level of 0.16 absorbance units was based on the examination of serum samples from 200 healthy controls. ELISA results were expressed as absorbance values obtained from a 1 : 200 dilution of the serum samples. Thirty patients with acrodermatitis chronica atrophicans (ACA) (Table I) were included as a positive control group (Fig. 1).

RESULTS

The distribution of the individual ELISA absorbance values and the median ELISA absorbance values in patients with scleroderma, granuloma annulare and PCT did not differ from the two control groups (Fig. 1). However, 2 patients with systemic sclerosis, 4 with localized scleroderma, one with granuloma annulare and one with sclerodermoid PCT were all seropositive. All samples from patients with ACA showed high absorbance values. None of the seropositive patients or controls had anamnestic or serological evidence of syphilis.

One of the seropositive patients with systemic sclerosis had been treated with penicillin for ACA 20 years earlier. A re-evaluation of patients and their medical records showed that 3 of the seropositive patients in the group with localized scleroderma and the one seropositive patient in the group with granuloma annulare had been misdiagnosed, and that their true diagnosis was ACA. Following antibiotic treatment, the skin lesions in these 4 patients cleared gradually and the antibody titres decreased significantly.

A short description is now given of the remaining 3 seropositive patients because, in spite of elevated antibodies against *B. burgdorferi,* we were unable to amend the diagnosis.

Case 1

The seropositive patient with systemic sclerosis was a 60-year-old woman with typical acrosclerosis (especially involving hands and face) and Raynaud's phenomenon for the last 20 years. During the last year, she developed a circumscribed infiltrated, erythematous area with sclerotic changes on the right thigh measuring 10×20 cm. The histopathology of two punch biopsies was typical of morphea. She had not been treated with antibiotics and could not recall any tick bites. She was treated with penicillamine 750 mg daily and, because of elevated antibodies against *B. burgdorferi*, with doxycycline 150 mg daily for 3 weeks. After 1 1/2 years the changes on the right thigh disappeared completely, but the acrosclerotic changes remained unchanged. A check on the absorbance value after 1 1/2 years showed a 40% reduction.

Case 2

The seropositive patient with localized scleroderma was a 73-year-old woman with typical localized scleroderma covering a

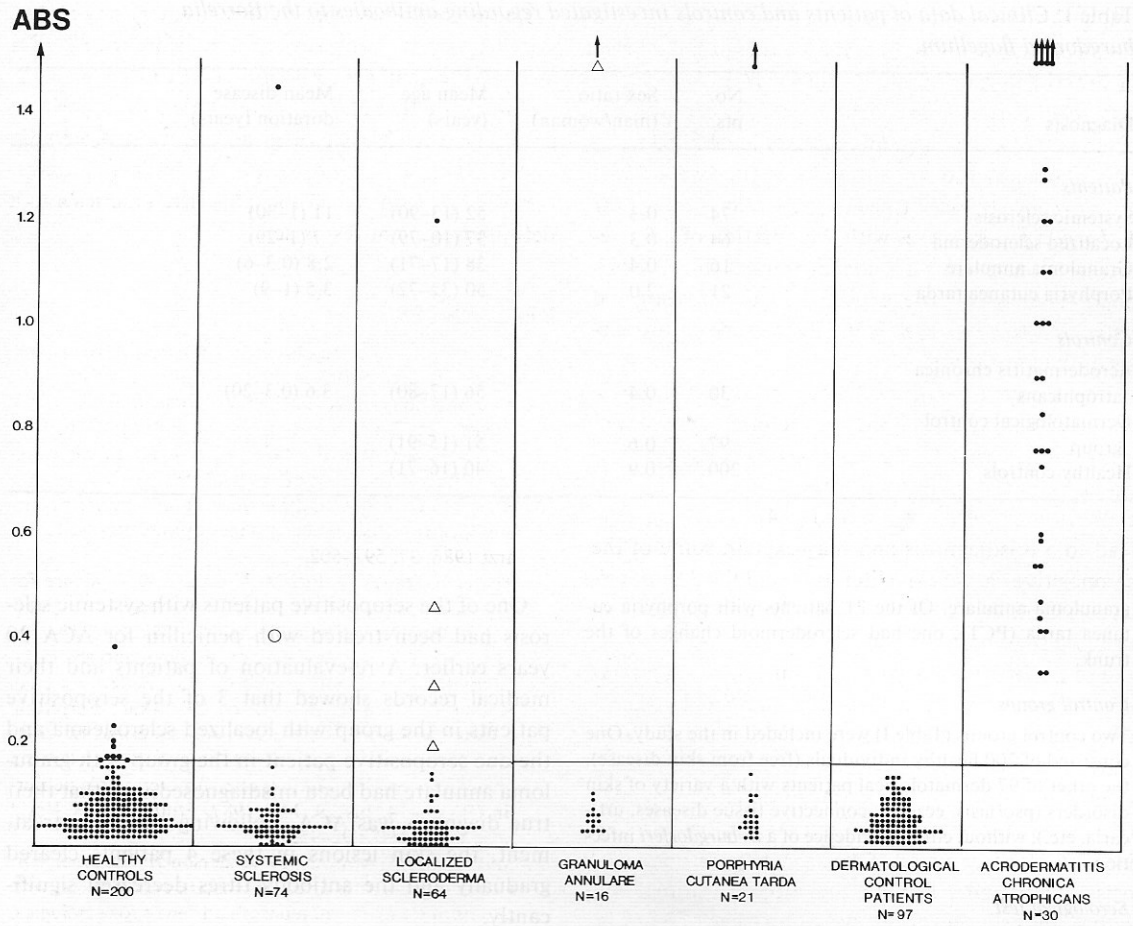

Fig. 1. IgG antibody levels measured by the Borrelia burgdorferi flagellum ELISA in sera from patients with systemic sclerosis, localized scleroderma, granuloma annulare and porphyria cutanea tarda, compared with healthy controls and patients with other dermatological disorders and patients with acrodermatitis chronica atrophicans. The horizontal line marks the 95% specific diagnostic cut-off level. △, Misdiagnosed patients; ○, a patient treated for ACA 20 years earlier.

larger area of the upper part of the trunk. The histopathological diagnosis was morphea. There was no history of a tick bite. She was treated with penicillamine 450 mg daily and topical steroids. Because of elevated antibodies against *B. burgdorferi,* penicillin 3 mill. daily was given for 10 days. The skin lesion gradually regressed during the subsequent 3 years, a check on the absorbance value after 1.3 years showing a 40% reduction.

Case 3

The seropositive patient with porphyria cutanea tarda was a 60-year-old man treated periodically with phlebotomies and hydroxychloroquine for the last 10 years. He had a history of chronic alcoholism. In addition he had alopecia areata and Tietze syndrome. Two years ago he noticed tightening and mottled hyperpigmentation of the skin of the face and the neck, with gradual spreading to the trunk and upper extremities. Microscopic examination of two punch biopsies showed histopathological changes typical of morphea and treatment with penicillamine 450 mg daily was started. One year ago, an elevated antibody titre against *B. burgdorferi* was found, and he was treated with penicillin 4.5 mill. daily for 3 weeks. During the following year the sclerodermoid changes slowly regressed. Early in 1988 he developed a transient AV-block and slightly elevated urinary uroporphyrin was demonstrated for the first time since 1986. The patient, who had hunted for many years, recalled more than hundred tick bites. A check on the absorbance value after 1 year showed a 56% reduction. In the summer of 1988 an inoperable malignant tumour of the lung was diagnosed and since then he has been lost to follow-up.

All samples from these 3 patients were tested and retested on the same plate.

DISCUSSION

In the present study we found no serological evidence of an etiological association between *B. burgdorferi* and scleroderma, granuloma annulare or porphyria cutanea tarda. The median antibody level in all three patient groups did not differ from the two control groups. Since the sensitivity of the serological tests for *B. burgdorferi* increases with the duration of a Borrelia infection, at least a tendency towards higher antibody levels should be expected in the investigated patients if *B. burgdorferi* is involved in the pathogenesis of these disorders.

The recognition of ACA may be difficult and a combination of clinical, histopathological and serological findings may be necessary to confirm the diagnosis. Furthermore, localized sclerodermatous changes may occur in ACA (1, 14). This fact may lead to a misdiagnosis and may explain some of the seropositive cases in the literature and the 3 seropositive patients in this report initially held to be localized scleroderma.

The positive serology obtained in 3 of our patients gives rise to special consideration. In patients 1 and 3 the primary skin disorders (acrosclerosis and PCT) started several years ago. Furthermore, following treatment with antibiotics, the acrosclerotic changes (Pat. no. 1) remained stable and urinary uroporphyrins (Pat. no. 3) recurred. A relation between acrosclerosis or PCT and a Borrelia infection therefore seems rather unlikely. However, we cannot exclude a relation between the localized scleroderma and a Borrelia infection in either patient.

It is impossible for us to state whether antibiotics, penicillamine, or time was the healer. Concerning patient No. 2, with localized scleroderma, the problem is the same, because the lesion regressed gradually over 3 years.

The discrepancy between our results and previous studies indicating 40–50% of patients with localized scleroderma to be seropositive (2, 3, 4) is most likely due to their use of too low and thus diagnostically unspecific cut-off levels. Other investigators who have used a similar whole-cell antigen assay but with a 95–100% specific diagnostic cut-off level could not find an increased prevalence of antibodies to *B. Burgdorferi* in localized scleroderma (9–11). The present study using the even more sensitive and specific *B. burgdorferi* flagellum ELISA (12, 13) confirms the lack of serological support for the hypothesis of an association of *B. burgdorferi* with localized scleroderma, granuloma annulare or porphyria cutanea tarda.

There is no doubt that a Borrelia infection—just as syphilis—can resemble several skin disorders. However, to state that a skin disorder is caused by a *B. burgdorferi* infection cannot rely solely on a positive antibody titre. The serological test must always be evaluated in association with the clinical findings, histological picture, IgG (or IgM) titre kinetics and a definite treatment response.

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