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CLINICAL REPORTS

Chilblains and Raynaud Phenomenon are Usually not a Sign of Hereditary Protein C and S Deficiencies

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Hereditary protein C and S deficiencies are risk factors for thrombosis. They are associated with purpura fulminans and coumarin-induced skin necrosis. Recently, necrotic livedo of the extremities, severe chilblains and severe frostbite have been observed in protein C or S deficient patients. Our study was designed to evaluate the prevalence of cold-induced acral manifestations in patients with protein C or S deficiency. One-hundred-and-six patients with protein C or S deficiency and controls matched for sex and age were studied by questionnaire. Data included any history of acral manifestation possibly related to cold exposure, i.e. chilblains, Raynaud phenomenon, acrocyanosis and possible associated factors. Assessment of the diagnosis by a dermatologist was recorded. No difference was found in the prevalence of acral manifestations between patients and controls. This study suggests that protein C and S deficiencies are not risk factors for cold-induced acral manifestations. ***Key word: acrosyndromes.***

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Proteins C and S function as major coagulation cascade regulators. Thus deficiency of protein C or protein S may promote a thrombotic state and is associated with arterial and venous thrombosis (1–3). Hereditary protein C and S deficiencies are also associated with several dermatologic conditions, including purpura fulminans, livedo reticularis and coumarin-induced skin necrosis (4–6). In the latter, thrombosis in microcirculation seems to be the most probable mechanism (7). It has been postulated that compromised blood flow due to low temperature prevailing in the skin may be of major importance for the induction of thrombosis (7). Necrotic livedo of the extremities has been reported in two cases of protein C deficiency (Gandon P and Vignon Pennamen MD, unpublished data). Recently, two adult patients attended our department with severe cold-induced acral manifestations: in the first, severe chilblains of hands and feet were diagnosed and a protein C deficiency was found. The second patient had severe frostbite associated with protein S deficiency. These clinical cases raise the question of whether cold-induced acral manifestations are associated with protein C or S deficiency. Our study was designed to evaluate the prevalence of cold-induced acral manifestations in patients with protein C or S deficiency when compared to a control population.

MATERIAL AND METHODS

One-hundred and six patients with protein S ($n=74$) or protein C deficiency ($n=32$) were included in the study. Fifty were propositii referred to the hemostasis and thrombosis unit for unexplained venous and/or arterial thrombosis. The remaining 56 patients were first-degree relatives investigated during familial inquiry. The diagnosis of protein S deficiency was based on protein S activity and/or free protein S antigen levels below 0.65 IU/ml (m-2 sd for the normal population) with normal C_4b-BP levels. Protein C deficiency was diagnosed when protein C amidolytic activity, chronometric activity and antigen level were below 0.65 IU/ml (m-2 sd for the normal population). Consecutive outpatients attending the dermatology department were asked for acceptance to be included as controls. Patients and controls were matched for sex and age.

A questionnaire was sent to each patient and analysed blindly. Data recorded included age, sex, any history of acral manifestation possibly related to cold exposure, i.e. chilblains, Raynaud phenomenon, acrocyanosis or unusual sensitivity to cold. Chilblains were defined as pruriginous erythematous lesions on fingers or toes appearing after cold exposure. Raynaud phenomenon was considered as definite when paroxysmal pallor of one or more digits was followed by cyanosis and erythema; it was considered possible when only the paroxysmal pallor phases was observed. Whether or not the diagnosis of chilblains or Raynaud phenomenon had been assessed by a dermatologist was specified. Acrocyanosis was considered when only cold-induced cyanosis was reported. Finally, patients were asked if they considered themselves as being unusually sensitive to cold. Any associated skin lesion related to cold was eventually specified. History of thrombosis, systemic lupus erythematosus, smoking habits, drug intake and occupational activity were noted. Controls were given a similar questionnaire. The chi-square test, with Yate's correction when needed, was used for statistical comparisons.

RESULTS

Among patients with proteins C and S deficiencies, 80 (74.5%) returned the questionnaire. No control refused to collaborate ($n=81$). Characteristics of patients and controls are listed in Table I. Prevalence of acral cutaneous manifestations due to cold exposure was not statistically different in the two groups. Characteristics of chilblains, i.e. related pruritus, location, duration, and seasonal variation were similar. The prevalence of acrocyanosis and of abnormal cold sensitivity was not statistically different in patients and controls.

In the patient group, 13 reported skin lesions appearing after cold exposure and localized on other sites than fingers and toes: skin dryness ($n=5$), redness of face ($n=2$), chapped hands ($n=2$), mottling of legs ($n=2$). Two patients related unspecified cutaneous cold-induced lesions. In the control group, similar lesions were found in 14 cases without difference between groups.

Two cases of systemic lupus erythematosus were noted in each group. Thirty-six patients had a history of thrombosis, in

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Table I. *Acral skin lesions due to cold exposure in patients with protein C and S deficiencies and controls*

	Patients	Controls
Number (Male/Female)	24/56	25/56
Age (years)	42.8 ± 16.7	41.1 ± 16.1
Chilblains (no.)	17	18 (22)
Assessed by dermatologist	4	3 (3.7)
With pruritus	9	12
Located on fingers only	6	11
on toes only	6	3
on fingers and toes	3	3
on face	1	0
Site not precised	1	1
Appearing in winter only	12	14
in winter and spring	3	1
in autumn only	1	0
in summer only	1	2
Duration (years)	9.6 ± 8.1	7.3 ± 7.6
Raynaud phenomenon		
Definite	1	1
Possible	10	6
Assessed by dermatologist	5	4
Acrocyanosis	5	2
Abnormal sensitivity to cold	30	28

contrast, as expected, with only four controls. Differences in drug intake were found only for anticoagulant therapy. In the patients group, the frequencies of chilblain, Raynaud phenomenon and acrocyanosis were not different whether or not the patients were anticoagulated. No patient and no control took drugs likely to induce Raynaud phenomenon. Occupational activities were similar in the two groups. There was no difference between the groups regarding current smokers (15 versus 18), ex-smokers (12 versus 9) and no smokers (49 versus 52).

DISCUSSION

In this study, no difference was found in the prevalence of acral manifestations related to cold exposure between patients with protein C or S deficiency and controls. It cannot be excluded that differences could have been found in a larger series. Possible methodology bias could have been introduced by differences in the recruitment of controls and patients. Indeed, controls had the questionnaire given in hand and patients had it mailed, explaining at least partially the 74.5% patient response. However, special care was taken not to interfere with the answer of the controls. Moreover, the two groups were similar when location, duration and seasonal variation of chilblains as well as associated skin lesions were considered. As expected, patients were taking anticoagulant more frequently than controls. Severity of the acral manifestations was not directly investigated by our questionnaire. However, the lack of difference in location and duration of chilblains makes a difference in severity unlikely.

Chilblains were reported by 21% of patients with protein C or S deficiency and in 22% of controls. This incidence is high. Hallam (8) found a prevalence of 5.3% in 1000 randomly selected patients but in agricultural workers using pesticides and servicewomen, chilblains were noted in 7 and 30% of individuals (9, 10). When we asked if the diagnosis of chilblains had been assessed by a dermatologist, their prevalence fell to 5%, which is close to the expected frequency in the general population. Our prevalence of abnormal sensitivity to cold and Raynaud phenomenon was similar to findings in the general population (11).

Protein C-deficient patients have an increased risk of developing a transient severe protein C deficiency associated with skin necrosis during the initial phase of oral anticoagulant therapy. The predilection of thrombosis for the microvasculature of the skin remains unexplained. However, even if thrombosis of dermal blood vessels is not a primary event in Raynaud's phenomenon, a compromised blood flow due to low temperature prevailing in the skin may be a worsening event in patients with protein C or S deficiency (7). Nevertheless, this hypothesis seems unlikely. Actually, acral manifestations are not strongly related to protein C or S deficiency.

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