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CLINICAL REPORT

Lupus Anticoagulant in Patients with Chronic Venous Insufficiency

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Chronic venous insufficiency is a widespread disease that can often lead to venous leg ulcers. Recent studies report that certain clotting abnormalities, such as anticardiolipin antibodies, are associated with leg ulcers. Although lupus anticoagulant belongs to the antiphospholipid antibodies, its presence in patients with chronic venous insufficiency has not been reported previously. The purpose of our study was to determine the presence of lupus anticoagulant in chronic venous insufficiency patients at a stage with no leg ulcers, and to follow the clinical outcome. In 37 patients with chronic venous insufficiency and in 54 control patients, lupus anticoagulant was evaluated using the Viper Venom Russell's Diluted Test. Lupus anticoagulant was found significantly more often ($p < 0.001$) in patients with chronic venous insufficiency than in controls. After 4 years, patients with chronic venous insufficiency with lupus anticoagulant were found to develop a venous leg ulceration more frequently compared to those without ($p = 0.01$), suggesting that lupus anticoagulant may play an important role in the pathogenesis of chronic venous insufficiency. *Key words: lupus anticoagulant; risk factor; venous insufficiency; venous leg ulceration.*

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Chronic venous insufficiency (CVI) is a common cause of leg ulcers (1). Its pathophysiology in large veins is well established. Deep or superficial veins become impaired, permitting reverse flow and resulting in venous hypertension (2, 3). It has recently been claimed that venous ulcers also develop as a consequence of fibrin cuff formation or leucocyte trapping (4–7). Furthermore, several studies have shown that clotting abnormalities such as protein C, S or AT III deficiency and anticardiolipin antibody (ACA) are associated with cutaneous ulcerations of the leg (8–12), and we recently demonstrated that patients with venous leg ulcers have lupus anticoagulant more frequently than controls do (13). Lupus anticoagulant belonging to the antiphospholipid antibodies is characterized as an anticoagulant *in vitro* but associated with excessive clotting *in vivo*. We therefore speculated that lupus anticoagulants may already exist in patients with CVI at a stage without present or previous ulcers, corresponding to stage II of the Widmer classification (14) and C_4, E_S, $A_{D;S;P}$ P_R according to the CEAP classification (15) (C_4 = skin changes without a present or previous ulceration; E_S = secondary venous disease; $A_{D;S;P}$ = involvement of deep veins, superficial veins, perforating veins; P_R = reflux). Hence, the purpose of our study was to investigate these patients with CVI stage II in regard to lupus anticoagulant. Additionally, the development of venous leg ulceration in patients with and without lupus anticoagulant has been evaluated over a period of 4 years.

MATERIAL AND METHODS

Study design

The study was conducted as a prospective study and was implemented at the Department of Dermatology, Wilhelminenspital, Vienna, Austria to evaluate the presence of lupus anticoagulant in patients with CVI stage II. The development of venous leg ulceration in patients with and without lupus anticoagulant was also evaluated.

Patients

Over a 4-month period (August to November 1998), 41 ulcer-free patients presenting with CVI stage II were referred to our department. Those receiving heparin or oral anticoagulants, or having a previous history of thrombosis and lupus erythematosus, were excluded, so that finally 37 patients were enrolled in the study. All 37 had a deep venous insufficiency with/without secondary superficial venous insufficiency. Venous refluxes were confirmed by Doppler ultrasound or duplex sonography, and all patients presented limbs with skin changes, including hyperpigmentation, dermatosclerosis, atrophia blanche and eczema. All patients received compression therapy with short stretch bandages or class II compression stockings.

Fifty-four patients referred to the Department of Dermatology during the same period, mainly for psoriasis, dermatitis and eczema, constituted the control group. None had a previous history of thrombosis, lupus erythematosus or anticoagulant therapy. Informed consent was obtained from all patients.

Follow-up

In November 2002, approximately 4 years after the initial examination, all patients were contacted via telephone, or were reinvestigated, in order to evaluate whether those with

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positive lupus anticoagulant develop a venous leg ulceration more frequently than those without.

Determination of lupus anticoagulant

Lupus anticoagulant was evaluated using the Viper Venom Russell Diluted Test (Dade Behring) in accordance with the manufacturer's instructions (16–18). The principle of this procedure is based on the fact that Russell's viper venom, phospholipids and calcium in the reagent directly activate factor X and factor V, thereby triggering the joint cascade of the intrinsic and extrinsic coagulation pathways. Any lupus anticoagulant contained in the sample prolongs the coagulation time, because it blocks the phospholipids necessary for the coagulation process. If the coagulation time is above the reference range, the LA 2 test is used for confirmation, as it contains an excess of phospholipids which neutralize the lupus anticoagulant. A BCS (Behring Coagulation System) machine was used for the test.

Statistical analysis

The chi-square test and U-test (Mann-Whitney) were used for statistical parameter testing. The level of significance was set at $p<0.05$. To evaluate the relation of lupus anticoagulant between the groups, the odds ratio (OR) and 95% confidence interval (CI) were calculated.

RESULTS

Patient-specific characteristics are summarized in Table I. There were no significant differences between groups in regard to age or sex ($p>0.05$). Of 37 patients with CVI stage II, 12 (32.4%) were shown to have lupus anticoagulant. In contrast, only 2 of 54 control patients (3.7%) had this abnormality ($p<0.001$).

Thirty-one of the 37 patients with CVI could be studied after 4 years; 6 were lost to follow-up (Table II). In the group of patients positive for lupus anticoagulant ($n=10$), 5 (50%) had developed a leg ulcer within the 4 years of follow-up. In the group of patients negative for lupus anticoagulant ($n=21$) only 2 (10.5%) had developed a leg ulcer within the 4 years of follow-up; significantly fewer than in those positive for lupus anticoagulant ($p=0.01$) (OR = 5.25, 95% CI 4.5–6.0).

In the control group, 48 out of 54 patients could be followed after 4 years; none of the patients developed a venous leg ulceration.

Table I. *Patient characteristics and presence of lupus anticoagulants in those with chronic venous insufficiency (CVI) compared with a control group*

	CVI ($n=37$)	Control group ($n=54$)
No. of patients (female %)	37 (70)	54 (65)
Mean age (years) (range)	54 (25–83)	55 (22–88)
Positive for LA (*n* (%))	12 (32.4)*	2 (3.7)

*$p<0.001$ compared with controls; LA: lupus anticoagulant.

Table II. *Association of lupus anticoagulant (LA) and the development of venous leg ulceration within 4 years of follow-up*

	Positive for LA ($n=10$)	Negative for LA ($n=21$)	Controls ($n=48$)
No. of patients with venous leg ulcer	5 (50%)	2 (10.5%)	0

DISCUSSION

CVI is a relevant social and health-care problem (19–21) affecting not only large veins, including venous refluxes leading to venous hypertension, but also the cutaneous microcirculation. In a study of the microcirculatory dysfunction in CVI, Junger et al. (22) showed that microangiopathic changes worsen in linear proportion to the clinical severity of CVI. Venous ulcers have also been reported to develop as a consequence of fibrin cuff formation or leucocyte trapping (4, 5), which leads to ulceration of the leg (6, 7). Lupus anticoagulant is possibly involved in this process by causing repeated microthrombi, which lead to chronic damage of the skin and eventually to poorly healing venous ulcers of long duration.

In the present study, lupus anticoagulant was found to be significantly associated with patients who had CVI at a stage without a present or previous leg ulcer.

Significantly more patients with CVI positive for lupus anticoagulant developed a leg ulcer within 4 years of follow-up compared to those without lupus anticoagulant. Lupus anticoagulant thus seems to be a risk factor for later development of venous leg ulceration. The question arises as to what therapeutic measures should be taken when the presence of lupus anticoagulants has been established. Further study investigating whether anticoagulation therapy prevents the development of leg ulcerations in those patients is needed.

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