OBJECTIVES: To study the prevalence of factor V Leiden mutation in patients with chronic venous insufficiency and venous leg ulcers, compared with a control group, and to find out whether factor V Leiden mutation is more frequent in patients with chronic venous insufficiency and a history of deep venous thrombosis.

Design: A case control study.

Setting: Three outpatient dermatological clinics.

Patients: Ninety-two patients (37 men, 55 women) with venous leg ulcers and 53 control patients (23 men, 30 women).

Main Outcome Measure: Factor V Leiden mutation.

Results: Factor V Leiden mutation was significantly more frequent in patients with chronic venous insufficiency and venous leg ulcers than in the control group (23% vs 7.5%; P = .03), and the patients with factor V Leiden mutation were more likely to have a history of venous thromboembolism (91% vs 48%, P = .002). Also, recurrent deep venous thrombosis (38% vs 14%) and recurrent leg ulcerations (9 episodes or more) occurred more frequently in the patients with factor V Leiden mutation (43% vs 19%, P = .01). No difference was observed in venous refill time or in the presence of dermatoliposclerosis and atrophie blanche.

Conclusions: Factor V Leiden mutation is more frequent in patients with venous leg ulceration than in the control group and the general population. Patients with factor V Leiden mutation have an increased risk of developing deep venous thrombosis and recurrent leg ulceration.

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VENOUS LEG ulceration is a significant health problem for both patients and clinicians. It forms the end stage of the complex of symptoms of chronic venous insufficiency (CVI). Epidemiological studies have estimated the prevalence of severe CVI to be between 6% and 8%, whereas 0.5% to 2% of the general population is affected by venous leg ulcers.

In 50% of patients with leg ulcers, a history of deep venous thrombosis (DVT) is present. In this group of patients, the diagnosis of venous thrombosis has often been based on “clinical signs and symptoms.” Only a limited percentage of patients suspected of DVT really had the disease. Their proportion is dependent on referral and selection.

Activated protein C (APC) resistance, as a frequently occurring hereditary risk factor for DVT, was first described by Dahlbäck et al in 1993. One year later, the genetic defect known as factor V Leiden mutation was identified by Bertina et al. The prevalence of the factor V Leiden mutation is estimated to be 5% to 6% in the general population in Europe and 3% to 5% in the Netherlands.

The activated form of coagulation factor V plays an important role in the generation of thrombosis. To prevent excessive thrombus formation, the activated form of coagulation factor V is inactivated by APC. This efficient negative feedback mechanism is disturbed in patients with factor V Leiden mutation because the mutation is located on one of the major APC-cleavage sites, leading to so-called APC resistance.

Heterozygous factor V Leiden mutation increases the risk of venous thrombosis 5- to 7-fold. Activated protein C resistance accounts for 20% of the cases of DVT and for 50% of the cases of familial venous thrombosis. Leg ulcers represent one of the most serious complications of the postthrombotic syndrome. For
PATIENTS AND METHODS

PATIENTS

During an 8-month period, 92 patients (37 men, 55 women; age range, 38-97 years) from the outpatient dermatological clinic of the University Hospital Maastricht, the Hospital De Tjongerschans in Heerlen, and Canisius Wilhelmina Hospital in Nijmegen, the Netherlands, were studied. All patients were treated for venous ulceration, classified as Widmer stage III (active venous ulcer or history of recurrent venous ulcer),1 The exclusion criterion was severe arterial insufficiency (ankle/arm index <0.6).

As a control group, 54 patients (age and sex matched) with isolated nonmetastasized, nonmelanoma skin malignancy (basal cell carcinoma and squamous cell carcinoma) without a history of venous leg ulceration were studied. Informed consent was obtained from all patients.

METHODS

A detailed history of venous thromboembolism (VTE) and leg ulceration was obtained in all selected patients. The presence of clinical abnormalities, such as dermatoliposclerosis, atrophie blanche, and hemosiderine pigmentation, was noted. Light reflex rheography was performed as described by Neumann and Boersma.16 A venous refill time of 20 seconds or less was considered abnormal. The characteristics of the patients are listed in Table 1.

The difference in the prevalence of factor V Leiden mutation between the patients and the controls was investigated. DNA was isolated from peripheral blood leukocytes by standard methods.5 The relevant region of exon 10 of the factor V Leiden gene was amplified by polymerase chain reaction. After amplification and subsequent digestion, the products were visualized on 2.5% agarose gels.5

STATISTICS

The results were statistically compared with those of Student t tests, Mann-Whitney tests, and χ2 tests. Confidence intervals (CIs) were calculated, especially for case control data, on the basis of a binomial distribution.17

screening APC resistance, functional coagulation tests, such as determination of activated partial thromboplastin time, can be used. The “gold standard” is polymerase chain reaction analysis of genetic DNA.13,15

The aim of this study was to investigate (1) the prevalence of factor V Leiden mutation in a large group of patients with CVI and venous leg ulcers; (2) whether factor V Leiden mutation is seen more frequently in patients with CVI, with or without a history of DVT; and (3) whether the prevalence of factor V Leiden mutation was higher in our group of patients than in the general population or in the control group.

RESULTS

Twenty-one of the 92 patients showed factor V Leiden mutation: 20 patients with a heterozygous pattern and 1 patient with a homozygous factor V Leiden mutation (Table 2). The difference in the prevalence of factor V Leiden mutation between the patients and the control group was rather small (26 patients). These differences clearly show the importance of DNA analysis in confirming the diagnosis of factor V Leiden mutation.

In our study, patients with a history of VTE were found more often in the group of patients with leg ulcers (23%) than in the control group (P = .03, χ2; odds ratio [OR], 3.6; 95% CI, 1.2-11.2).

In patients with factor V Leiden mutation, a history of VTE was more frequent (91% vs 48%; P = .002, χ2). A history of recurrent DVT was present in 8 (38%) of 21 patients with factor V Leiden mutation and in 10 (14%) of 71 patients without factor V Leiden mutation (P = .03; OR, 3.8; 95% CI, 1.2-11.3). Factor V Leiden mutation was associated with an increased prevalence of venous leg ulceration: there were 9 or more episodes of ulceration in 9 patients (43%) with factor V Leiden mutation and in 11 patients (16%) without the mutation (P = .01; OR, 4; 95% CI, 1.4-12.0). There was no association between recurrent DVT and the number of recurrences of leg ulceration or between factor V Leiden mutation and the presence of atrophie blanche or dermatoliposclerosis. The average age of the patients with factor V Leiden mutation was not different from that of the other patients. The average venous refill time was the same in both groups (8.9 seconds vs 8.7 seconds).

COMMENT

Chronic venous insufficiency resulting in leg ulcers has a large impact on quality of life.18 The present study shows a significantly increased prevalence of factor V Leiden mutation of 23% in patients with venous leg ulcers, compared with a prevalence of 7.5% in the control group (P = .03, χ2). Our study results confirm the recently reported APC resistance rate of 26% in patients with venous leg ulcers.19 In the study by Munkvad and Jorgensen,20 gene mutations were not investigated. Another study, by Grossman et al,19 found a much lower prevalence of factor V Leiden mutation (7.7%). However, their patient group was rather small (26 patients). These differences clearly show the importance of DNA analysis in confirming the diagnosis of factor V Leiden mutation.

In our study, patients with a history of VTE were found mostly in the mutated factor V Leiden patient group. These
results suggest that patients with the combination of VTE and factor V Leiden mutation have an increased risk of developing venous leg ulcers. However, the fact that the clinical history with respect to DVT is not always reliable should be taken into consideration. In the past, duplex sonography was not available, and other techniques, such as phlebography and impedance plethysmography, were certainly not routinely used in all cases. To date, there are no additional diagnostic procedures, such as photoplethysmography, which is an accepted screening method for the hemostatic consequences of CVI, to predict increased risk for leg ulcers, since venous refill time was the same in both patient groups. The association between recurrent leg ulceration of more than 9 episodes and factor V Leiden mutation indicates that the presence of factor V Leiden mutation represents a high risk for recurrent venous ulceration.

Recurrent venous thrombosis was 3 to 4 times more frequent in the group of patients with factor V Leiden mutation. These data support the hypothesis that patients with factor V Leiden mutation may require prolonged anticoagulation therapy, as suggested by Ridker et al. They reported a 4- to 5-fold increased risk of recurrent venous thrombosis in patients with factor V Leiden mutation, whereas others did not observe such an increased risk. As a control group, patients with solitary uncomplicated skin malignancies were studied. Although these individuals do not represent the “healthy” population, no increased prevalence of DVT is seen in this group of patients, as opposed to patients with internal or metastasized malignancies. It should be taken into account that the patients with CVI seen by us in the outpatient clinic are patients with more severe complications; they might not be representative of all patients with venous leg ulcers.

Besides venous thrombosis in macrocirculation, microthrombi in microcirculation are thought to play an important role in the pathogenesis of venous leg ulcers. It is not unlikely that during ulceration microthrombi are formed and that thrombotic events in macrocirculation and in microcirculation are related. The high percentage of factor V Leiden mutation in patients with venous leg ulcers supports this theory.

The role of compression therapy and anticoagulation in preventing postthrombotic complications should be considered. The importance of continuing compression therapy for 2 years after DVT has been diagnosed has recently been demonstrated. The rate of postthrombotic syndrome was reduced by 50% by the use of compression stockings.

Lower rates of recurrent idiopathic DVT during 6 months of oral anticoagulant therapy, instead of 6 weeks, support the hypothesis that patients with DVT and factor V Leiden mutation may require an increased period of anticoagulant therapy. Long-term aspirin therapy in the group of patients with recurrent leg ulcers might decrease the risk of recurrent ulceration. Additional trials of low-molecular-weight heparin and aspirin therapy are necessary to study the reduction of these postthrombotic complications.

We conclude that factor V Leiden mutation is more frequent in patients with (recurrent) venous leg ulceration than in the general population. Patients with a factor V Leiden mutation have an increased risk of developing DVT and recurrent venous leg ulcers. Further studies are necessary to prove the importance of prolonged anticoagulant and compression therapy in decreasing the risk of VTE and postthrombotic complications.

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Reprints not available from the authors.

Table 2. Prevalence Rates of (Recurrent) Venous Thromboembolism (VTE), Number of Leg Ulcers, and Clinical Characteristics in Patients With Venous Leg Ulcers With (Group 1) and Without (Group 2) Factor V Leiden Mutation

<table>
<thead>
<tr>
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<th>Group 1</th>
<th>Group 2</th>
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<tbody>
<tr>
<td>No. (%) of patients</td>
<td>21 [12/9] (23)</td>
<td>71 [25/46] (77)</td>
</tr>
<tr>
<td>No. (%) of patients with a history of VTE†</td>
<td>8 (38)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Average age (range), ‡</td>
<td>65.0 (39-97)</td>
<td>69.2 (38-90)</td>
</tr>
<tr>
<td>No. of leg ulcers in past (range)‡</td>
<td>7.0 (1-20)</td>
<td>5.8 (1-20)</td>
</tr>
<tr>
<td>No. of patients with &gt;9 ulcers in past§</td>
<td>9 (43)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Light reflex rheography (range), s‡</td>
<td>8.4 (4-19)</td>
<td>8.7 (4-20)</td>
</tr>
<tr>
<td>No. (%) of patients with dermatoliposclerosis¶</td>
<td>17 (81)</td>
<td>52 (73)</td>
</tr>
<tr>
<td>No. (%) of patients with atrophie blanches¶</td>
<td>10 (48)</td>
<td>42 (59)</td>
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* Significant difference between groups 1 and 2: P = .002.
† Significant difference between groups 1 and 2: P = .03.
‡ Not significant in either group.
§ Significant difference between groups 1 and 2: P = .01.
¶ Information on this condition was not available for 2 patients in group 1 and 8 patients in group 2.
†† Information on this condition was not available for 2 patients in group 1 and 13 patients in group 2.

REFERENCES