Thrombosis risk in systemic lupus erythematosus: The role of thrombophilic risk factors

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Thrombosis risk in systemic lupus erythematosus: the role of thrombophilic risk factors

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Objectives: Thromboembolic episodes are frequent manifestations of systemic lupus erythematosus (SLE). Although the presence of anti-phospholipid antibodies (aPL) is known to contribute to thromboembolism (TE), the relative contribution of other TE risk factors is unknown. The aim of this study was to determine the prevalence of TE in a Caucasian SLE population, to identify the risk factors of highest importance, and to assess the clinical value of thrombophilia screening among SLE patients.
Methods: Samples from 105 patients were analysed with a screen including aPL, activated protein C resistance, factor V Leiden (FVL) and prothrombin G20210A mutations; protein C, protein S and antithrombin activity; factor VIII (FVIII) and von Willebrand factor (vWF), and homocysteine (Hcy) levels.
Results: The annual incidence of arterial and venous TE events in our SLE population was 5.4 and 12.4 per 1000, respectively. The highest risk of thrombosis was carried by the simultaneous presence of lupus anticoagulant (LA) and anti-cardiolipin (aCL) [relative risk (RR)=4.03, 95% confidence interval (CI) 2.06–7.86] or anti-β2-glycoprotein I antibodies (aβ2-GPI) (RR=5.10, 95% CI 2.58–10.1). Positivity for the individual aPL tests all carried an elevated TE risk. The presence of other risk factors seemed to be of less importance.
Conclusions: In SLE patients, the presence of aPL is a more significant risk factor for the development of thrombosis than the known inherited deficiencies. Based on these data, routine screening for additional hereditary risk factors seems to be unwarranted.

Systemic lupus erythematosus (SLE) is an autoimmune disease with diverse clinical and laboratory manifestations. Its main characteristics include the presence of a wide range of pathogenic autoantibodies, and an inflammatory response affecting many organs.

Phospholipids and associated glycoproteins are often targets of the antibodies produced in SLE (1). Several mechanisms triggered by the anti-phospholipid antibodies (aPL) are thought to contribute to the development of both venous (VTE) and arterial thromboembolism (ATE) (2–4). The antibodies attached to the negatively charged phospholipid surface may induce platelet activation, initiating the formation of a thrombus. Later, the antibodies occupying the phospholipid surface prohibit the binding of coagulation inhibitors, such as tissue factor pathway inhibitor (TFPI) or the protein C–protein S complex, thereby promoting thrombus growth. The binding of antibodies to the anionic phospholipid surface disrupts the protective shield of the anticoagulant protein annexin V, leading to the exposure of anionic phospholipids and accelerating coagulation reactions. Moreover, the phospholipid-recognizing autoantibodies effectively activate endothelial cells, inducing the expression of tissue factor and adhesion molecules ICAM-1 (intercellular cell adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1) and P-selectin.

Inflammation, another characteristic element of lupus, may affect several steps in blood coagulation: initiation, propagation and regulation (5). Inflammatory mediators increase the plasma level of blood-borne tissue factor (6), the exposure of negatively charged phospholipid membrane surfaces, and down-regulate protein C activation. Free protein S levels may be decreased by the complement regulatory protein C4BP (C4b-binding protein), which forms a complex with protein S in the circulation. C4BP plasma levels are often elevated during the inflammatory response.

Thus, patients with SLE are predisposed to cardiovascular diseases (7). However, inherited factors independent of SLE may also increase the risk of TE (8, 9).

Factor V Leiden (FVL) and Factor II G20210A mutations (10, 11) are the most common inherited

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risk factors for venous thrombophilia in the general population. Incidences of these mutations in Hungary in unselected controls were found to be 6.5–9.8% and 2.7–4.8% (12–14), respectively. Protein C, protein S and antithrombin deficiencies (15–17) are rare, but carry a higher risk for venous TE (18, 19). In addition to a defective anti-coagulation system, hypercoagulability may be induced by elevated levels of coagulation factors VIII, IX, XI, II (prothrombin) and I (fibrinogen) (18, 20). Among these, the increased plasma level of FVIII has been reported most frequently to have an impact on the development of thrombosis (21, 22).

Hyperhomocysteinaemia, which is in most cases an acquired deficiency, contributes to the development of arterial as well as venous thromboses (23) through promoting oxidative stress-mediated endothelial damage, activating blood cells, and inhibiting the binding of the anticoagulant proteins to their cofactors. Of note, homocysteine (Hcy) levels have been reported to be elevated in SLE (24).

The aim of our study was to determine the prevalence of thromboembolic events in a Hungarian patient population with SLE, to identify significant risk factors, to determine the relative risk associated with these factors, and to assess the clinical value of screening for thrombophilia in SLE.

Patients and methods

During a 12-month period, 105 consecutive SLE patients were enrolled in the study after providing informed consent: 99 females, six males; mean age 41.0 ± 11.7 years, age range 18–68 years; mean disease duration 14.6 ± 9.1 years. All patients were followed at the Outpatient Clinic for Immunology at Semmelweis Medical University, Budapest, and fulfilled the revised criteria of the American College of Rheumatology (ACR) for SLE (25). Clinical data including TE events were obtained retrospectively from records kept by the treating physician. Information was sought about the date and localization of previous TE, TE episodes in the families, medications such as anticoagulant therapy, previous and present use of oral contraceptives, etc.

SLE Disease Activity Index (SLEDAI) scores (26) for the date of sample collection was calculated to characterize disease activity.

Sera, plasma and DNA samples from all patients were analysed with the following tests.

The presence of aPL was investigated using two types of assays. First, lupus anticoagulant (LA) was detected by coagulation methods in a three-step screening and confirmation system. Screening with three independent tests (dPT 1:200, Innovin, Dade Behring, Germany; PTT-LA, Diagnostica Stago, France; dRVVT Screen, Gradipore, USA) was followed by phospholipid neutralization (Staclot LA, Diagnostica Stago and dRVVT Confirm, Gradipore). Second, aPL were measured by enzyme-linked immunosorbent assays (ELISAs), including an anti-cardiolipin (aCL) screen confirmed by aCL immunoglobulin G (IgG) and IgM, as well as the anti-β2-glycoprotein I (aβ2-GPI) IgG/IgA/IgM, anti-prothrombin (aFII) IgG/IgA/IgM, anti-phosphatidyl-serine (aPh-Ser) IgG/IgA/IgM screens (Orgentec, Germany). Normal ranges were defined as recommended by the manufacturer.

Protein C (PC) (Chromogenix, Italy), protein S (PS) (Dade Behring, USA), and antithrombin (AT) (Sigma, USA) activity were determined quantitatively by a Sysmex CA-1500 coagulometer. Normal ranges were 70–149% for PC, 59–118% (females) and 75–130% (males) for PS, and 50–150% for AT. Activated protein C resistance (APCR) was investigated by a commercial coagulation assay (Chromogenix, Italy). This assay uses FV-deficient plasma for sample dilution.

Melting curve analyses with polymerase chain reaction (PCR) were performed for Factor V G1691A 'Leiden' mutation and Factor II (prothrombin) G20210A mutation detection (Roche, Switzerland).

Factor VIII (FVIII) was measured by a microplate endpoint method (Chromogenix, Italy).

von Willebrand factor antigen (vWF:Ag) and collagen-binding activity (CBA) levels were measured by an in-house ELISA. Normal ranges for FVIII, vWF:Ag and CBA were 50–150%.

Plasma Hcy was determined by fluorescence polarization immunoassay (FPIA; Abbott, Norway). Plasma Hcy level was considered to be elevated over 15 μM.

Statistical analysis

Data obtained from each assay were first analysed by descriptive statistics. The average annual incidence of TE in SLE was calculated by dividing the number of first TE events by the number of patient years, defined as the period from onset of SLE until the end of the observation period, or the first episode of TE. To characterize the effects of the risk factors on the incidence of TE, relative risks (RRs) and odds ratios (ORs) with a 95% confidence interval (CI) were calculated for single as well as for multiple risk factors. An effect was defined as significant if the 95% CI did not include 1. OR values were confirmed by logistic regression analysis performed using the commercially available software MedCalc. With this analysis, an effect was significant if the criteria '$p < 0.05$' was fulfilled. There was no discrepancy between the two methods. For the sake of simplicity, RR values are given in the Results section.

Results

Epidemiology of TE episodes in our SLE population

Of the 105 SLE patients, 22 (21%) had a history of TE (Table 1). Seventeen patients had venous thrombosis; 14 of the 17 venous episodes were deep-vein thromboses (DVT), all but one in the lower extremity. Five of these patients subsequently had recurrent events. Two patients had superficial thrombosis, and a young patient had cerebral venous thrombosis. Eight patients had arterial thrombosis, all of them in the central nervous system. Three of the eight patients had both ATE and VTE.

There was no significant difference between patient ages at the onset of ATE and VTE events (40.1 ± 14.9 and 33.1 ± 10.8, respectively; $p=0.26$). Twenty-two first TE episodes occurred in 1335 patient years, thus the annual incidence of first thrombosis among our SLE patients was 16.5 per 1000. The incidence of first arterial events was 5.4 per 1000, while the incidence of first venous episodes was 12.4. At the time of sample collection there was no difference ($p=0.52$) in disease activities expressed as SLEDAI between the two groups: patients with (3.3 ± 3.7, range 0–16) and without (2.8 ± 3.0, range 0–14) a history of TE.

Anti-phospholipid antibodies

We found that 25.7% of the patients were positive for the aβ2-GPI ELISA test, and 21% (22 patients) were positive for the aCL ELISAs. Ten of the 22 positive patients had IgG aCL, two patients had IgM aCL, while the remaining 10 patients had both IgG and IgM aCL. The prevalences for aPh-Ser and aFII were 21% and 17.1%, respectively (Table 2).

Of the 105 SLE patients, 35.2% had detectable LA. The results of the coagulation assay and the ELISA tests overlapped significantly. Twenty-four patients (64.9% of the LA positive group) were positive for both aPL ELISA and LA. The number of positive ELISA test types influenced the probability of the simultaneous presence of LA. We found that 17.8% of the ELISA negative patients had LA, 50% and 66.7% of the patients with one and two positive aPL ELISAs, respectively, and 77.8% and 80% of the patient group with three and four positive aPL ELISAs, respectively. None of the ELISA tests or test combinations showed an exclusive association with LA (Table 3). However, we note that seven of nine samples with single aCL ELISA positivity and only one of five samples with single aFII ELISA positivity had LA activity.

Thus, some form of aPL was shown to be present in samples from 45 patients. Eighteen of the 45 patients with aPL (40%) had TE (six arterial and 14 venous events), while only four of the 60 aPL-negative patients (6.7%) had TE (two arterial and three venous events) (Figure 1).

The positivity for aCL or aβ2-GPI ELISAs carried higher risk for thrombosis than aFII or aPh-Ser (Table 3). The highest relative thrombosis risk within the whole SLE population was associated with the simultaneous positivity for aβ2-GPI and LA (RR=5.1, 95% CI 2.58–10.1).

Contribution of other TE risk factors to the risk of developing TE in SLE

Natural anticoagulant proteins. One patient had decreased PC activity (29%) and another patient had moderately decreased PS activity (46%). Neither of them had a thrombotic event. Sixteen patients received coumarin anticoagulant therapy, and were therefore excluded from PC and PS analysis. One patient without thrombosis had moderately decreased antithrombin activity (48%). No significant difference was found between the average AT levels of the patients with and without thrombosis (114.0 ± 24.9 and 105.1 ± 33.2, respectively; $p=0.26$).

Table 1. Clinical characteristics of the 105 SLE patients.

	Without TE	With TE
No. of patients	83	22
Women	78 (94.0%)	21 (95.5%)
Age (years)	40.6 ± 11.6 (18–98)	42.6 ± 12.2 (19–64)
Age at diagnosis (years)	26.3 ± 10.1 (3–64)	26.8 ± 10.8 (10–47)
Duration (years)	14.3 ± 9.2 (1–37)	15.9 ± 9.0 (4–31)
SLEDAI score at sample collection	2.8 ± 3.0 (0–14)	3.3 ± 3.7 (0–16)
VTE	–	17
ATE	–	8
$2 \leqslant$ foetal losses or pre-eclampsia	–	2
Anticoagulant therapy	1*	18
TE events on anti-coagulation	–	1

SLE, systemic lupus erythematosus; TE, thromboembolic episodes; SLEDAI, SLE Disease Activity Index; VTE, venous thromboembolic events; ATE, arterial thromboembolic events. *After prosthetic valve replacement.

Table 2. Thrombosis risk for different anti-phospholipid test types and test combinations.

	n	ATE	RR (ATE)*	VTE	RR (VTE)*	RR (95% CI)*
aCL	22	3	4.09 (0.73–22.87)	9	8.18‡ (2.44–27.49)	8.18‡ (2.95–22.71)
aβ2-GPI	27	5	5.56 (1.15–26.86)	10	7.41† (2.21–24.78)	7.78‡ (2.82–21.44)
aFII	18	2	3.33 (0.50–22.02)	4	4.44 (1.09–18.05)	5.00† (1.58–15.80)
aPh-Ser	22	3	4.09 (0.73–22.87)	8	7.27† (2.12–24.97)	6.82‡ (2.38–19.52)
No aPL by ELISA or LA	60	2	1	3	1	1
One aPL positive by ELISA	4	1	7.5 (0.85–66.13)	0	–	3.75 (0.54–26.19)
Two aPL positive by ELISA	9	1	3.33 (0.34–33.11)	5	11.11‡ (3.19–38.71)	8.33‡ (2.74–25.35)
Three aPL positive by ELISA	9	2	6.67 (1.07–41.58)	3	6.67† (1.58–28.10)	6.67† (2.02–22.04)
Four aPL positive by ELISA	10	1	3.00 (0.30–30.08)	3	6.00 (1.40–25.67)	6.00† (1.78–20.19)
Any aPL positive by ELISA	32	5	4.69 (0.96–22.82)	11	6.88† (2.07–22.88)	7.03‡ (2.55–19.42)
Positive (LA)	37	6	4.86 (0.63–37.28)	12	6.49† (1.96–21.47)	6.49‡ (2.35–17.92)
Positive aPL by ELISA and LA	24	5	6.25 (0.79–49.37)	9	7.50† (2.22–25.35)	8.13‡ (2.94–22.44)
aCL + aβ2-GPI + LA	16	3	5.66 (1.03–30.86)	6	7.50† (2.10–26.75)	8.44‡ (2.98–23.89)

n, the number of positive patients; ATE, VTE, the number of arterial and venous events, respectively, among the positive patients; RR, relative risk; aFII, anti-prothrombin; aPh-Ser, anti-phosphatidyl-serine; CI, confidence interval; aPL, anti-phospholipid antibodies; LA, lupus anticoagulant; aCL, anti-cardiolipin; aβ2-GPI, anti-β2-glycoprotein I. *RR compared to the patient group without any aPL. †$p<0.01$. ‡$p<0.001$.

The FV Leiden and FII G20210 mutations. Ten patients showed increased APCR due to the Leiden mutation. One of them had a homozygous defect, while another one was compound heterozygous for the Leiden and prothrombin G20210A mutations. Finally, one patient was heterozygous for the prothrombin G20210A mutation. Four of the 10 patients with Leiden mutation and the patient heterozygous for the prothrombin mutation had TE events, deep venous thromboses in all cases. However, the homozygous Leiden mutation and the compound heterozygous state for the two mutations did not lead to TE events in the two affected patients.

Acquired APCR. One patient with a history of recurrent arterial thrombosis was found to have acquired APCR that is he showed increased resistance to activated PC without the presence of mutations in factor V at the regions of arginines 306, 506 or 679. The sample of this patient showed high-titre positivity for all the aPL tested by ELISA as well as for LA. Acquired APCR (detected in undiluted samples) secondary to LA in SLE patients has been described previously (27). This patient is unique in that LA-affected APCR was detected in a system thought to be highly specific for the Leiden mutation.

To test whether LA might have an effect on our APCR detection system, we analysed data for the entire SLE group. No significant difference was found between the APCR ratios of patients positive for LA and negative for LA (2.39 ± 0.39 and 2.46 ± 0.28, respectively; $p=0.34$). Patients with Leiden mutation were excluded from this analysis.

FVIII and vWF. Ten of the 105 patients had elevated FVIII and vWF levels. Four of them had thrombosis; three venous and two arterial events. Another 11 patients (three of them with a history of TE) had elevated FVIII levels without increased vWF, and two patients (one of them with a history of TE) had elevated vWF with normal FVIII. Thus, elevated FVIII levels do not carry a statistically significant TE risk (RR=1.87, 95% CI 0.87–3.99). Similarly, the combined elevation of FVIII and vWF has no statistically significant effect (RR=2.11, 95% CI 0.89–5.02). Patients with a history of TE as a group were found to have vWF levels comparable to the group without TE (118.4 ± 53.6 and 98.1 ± 41.9, respectively; $p=0.11$).

Table 3. Comparison of the anti-phospholipid ELISA test types. Relative thrombotic risk of the patients with positive tests compared to the anti-phospholipid negative patients' risk (first column) and within the whole SLE population (second column) are shown, as well as the proportion and relative thrombotic risk of the patients also positive for lupus anticoagulant (LA).

	RR (95% CI)*	RR (95% CI) in the whole SLE group**	LA (%)	RR (95% CI) with LA**
a-cardiolipin	8.18‡ (2.95–22.71)	4.53‡ (2.26–9.07)	81.8	4.03‡ (2.06–7.86)
a-β2-glycoprotein I	7.78‡ (2.82–21.44)	5.06‡ (2.39–10.71)	74.1	5.10‡ (2.58–10.1)
a-prothrombin	5.00† (1.58–15.80)	1.81† (0.82–3.99)	66.7	2.91† (1.41–5.91)
a-phosphatidyl-serine	6.82‡ (2.38–19.52)	3.14† (1.57–6.30)	77.3	4.31‡ (2.23–8.34)

ELISA, enzyme-linked immunosorbent assay; SLE, systemic lupus erythematosus; RR, relative risk; CI, confidence interval. *RR compared to the patient group without any anti-phospholipid antibodies; **RR within the whole SLE group †$p<0.01$. ‡$p<0.001$.

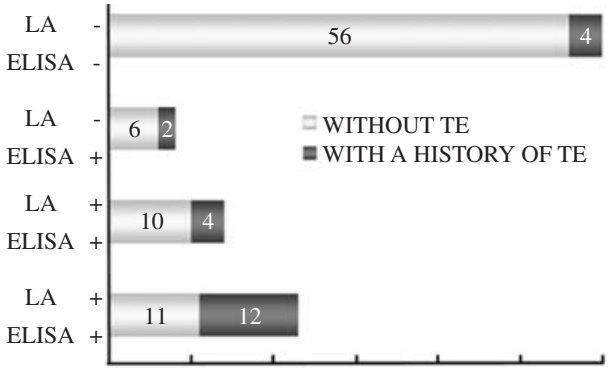

Figure 1. The number of persons with positive and negative thromboembolic (TE) history in four patient groups according to the presence of lupus anticoagulant (LA) and antiphospholipid antibodies (aPL) detected by ELISA. The simultaneous positivity for LA and APAs represents the highest thrombosis risk, while only a low proportion of patients negative for aPL detected by ELISA or by coagulation assay have already had thrombosis.

Hcy. Six of the 20 patients with elevated Hcy had a history of TE. One of these patients had arterial thrombosis, two had both arterial and venous events, and another three had venous TE episodes. This does not represent a significantly elevated TE risk (RR=1.59, 95% CI 0.71–3.55). Of the 20 patients with elevated Hcy, six (three women and three men) had Hcy levels above 20 μM; only one of them had an arterial thrombosis. No difference was found between the Hcy levels of the patients with or without a history of TE (12.2 ± 4.3 and 11.5 ± 4.6, respectively; p=0.53).

Does the presence of an inherited risk factor in addition to aPL predict a higher thrombosis risk?. The presence of either FVL, elevated FVIII or Hcy in addition to a positive aPL test only increased the relative risk of thrombosis slightly (from 1.3 to 1.4), which, in our patient population of 105, did not reach the level of statistical significance (data not shown).

Discussion

As cardiovascular diseases are the leading cause of death in the Western population, it is not surprising that thromboses, infections and active lupus were found to be the main causes of death among European SLE patients (28). Inflammation and the presence of aPL place SLE patients in a high-risk group for developing TE. Arterial and venous thromboses occur more often and at a younger age in those affected with SLE compared to the general population.

The incidence of new arterial and venous TE episodes in our SLE population was 5.4 and 12.4 per 1000, respectively. A similar overall incidence of venous events (13 per 1000) and a somewhat higher frequency of arterial episodes (16 per 1000) were reported in a recent study of SLE patients among three ethnic groups (Chinese, African Americans and Caucasians) (29).

In the present study, 21% of SLE patients had a history of TE. In previous reports with Caucasian patients of the same age distribution this ratio was reported to be 20–37% (9, 24), while 9.2% of a cohort of 1000 European SLE patients had TE events during a 10-year follow-up (28).

The age at onset of the arterial and venous TE events was lower in our SLE population (40.1 and 33.1 years, respectively) than that of the general population (30, 31). However, unselected patients with anti-phospholipid syndrome developed thrombosis at similar ages (35.0 and 34.5 years, respectively) (32).

The analysis of individual TE risk factors showed that the presence of aPL carries the highest thrombosis risk in our SLE population.

Among our SLE patients, the prevalence of LA (35.2%) and the various types of aPL detected by ELISA (17.1–25.7) was not different from that reported previously for aCL (12–60%), aβ2-GPI (20–30%), aFII (15–40) or aPh-Ser antibodies (20–40%) (9, 24, 33–40).

Positivity for LA or for the solid-phase aPL assays represents an approximately four- to fivefold increase in TE risk. The presence of the aCL, aβ2-GPI antibodies or the LA showed the strongest effect, while the presence of the aFII antibodies had the weakest effect on the development of TE (Table 3). A stronger association between TE and medium-high titres of aCL and aβ2-GPI antibodies and a lower clinical value of the aFII test have been described previously (39, 40).

Our results confirm the well-known relationship between the presence of aPL and the development of TE. However, while 30% of our SLE patients with aPL as a single risk factor had TE, this ratio was 50% among patients with additional risk factors as well.

To appreciate the cooperative nature of inherited thrombophilia risk factors and aPL, we considered patients with FV Leiden mutation, elevated FVIII or Hcy levels with or without the additional presence of aPL. As shown in Figure 2, patients with double risk factors had a higher frequency of thrombosis. The inherited thrombophilia risk factors had a milder effect on the development of TE events in SLE patients (Table 4) compared to that of the general population due to the strong effect of the presence of aPL. For example, we confirmed that the FVL mutation carries an increased relative risk for thrombosis (RR=5.17, 95% CI 1.18–22.61) within the group of patients negative for the LA. However, in the patient group with positive LA, this effect was statistically negligible (RR=1.18, 95% CI 0.41–3.39).

In our SLE patient population, the frequency of the FVL mutation and the prothrombin mutation

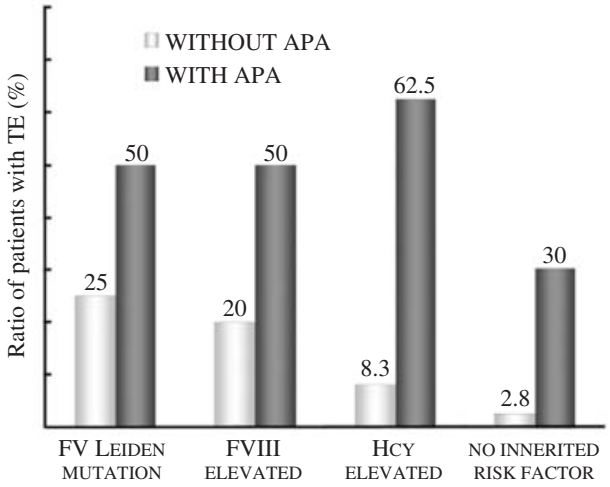

Figure 2. The contribution of the antiphospholipid antibodies (APAs) to the development of thromboembolism (TE) in the presence of other risk factors. 25 % of the patients with the factor V Leiden mutation had thrombosis in the APA negative patient group, while 50 % in the APA positive group. Similar effect can be observed in the patient groups with elevated plasma homocysteine or factor VIII levels; or among the patients without any detected risk factors.

G20210A (9.5% and 1.9%, respectively) was not different from those reported previously in unselected Hungarian patients (11–13). The frequency of the FVL in Hungary has been found to be higher than that in most of the other European populations (41, 42).

The frequency of FVIII levels above 150% among our patients with a history of TE was 31.8%, while among those without TE was 16.9%. These ratios are somewhat higher than those (25% vs. 11%) from a study comparing 301 general VTE patients and 301 healthy individuals (43).

Moderate hyperhomocysteinaemia was previously described to be present in 28.8% of Caucasian DVT patients and 11.5% of patients without thrombosis (44). In our SLE population these ratios were similar, at 27.3% and 16.9%.

As the different deficiencies act at different sites of the coagulation system, the clinical nature of thrombosis can also vary with the type of defect.

Four of the 10 patients with the Leiden mutation had a history of TE. All of these patients had DVT. Conversely, five of nine patients with LA and elevated plasma Hcy experienced three arterial and four venous events. Among these patients, the risk of arterial thrombosis was higher than the risk of venous thrombosis (RR=6.4, 95% CI 1.82–22.51 vs. RR=3.28, 95% CI 1.35–7.98). However, our data showed that the presence of aPL contributes equally to the development of arterial and venous events. Positivity for the aPL represented comparable RR for ATE and VTE (Table 2).

The two patients with superficial thrombophlebitis had aPL as their single risk factor. Although this kind of thrombosis is often associated with inflammatory states, these two patients had inactive SLE at the time of the development of their thrombophlebitis. A young female patient with cerebral venous thrombosis presented with high titres of all aPL and the LA as her single risk factor. Cases of young patients with cerebral venous thrombosis associated with LA have been reported previously (45, 46).

About one-third of the TE episodes (25% of the arterial, 35.3% of the venous events) occurred within the first 2 years after the diagnosis of SLE; another third (37.5% and 29.4%) occurred between the second and tenth year after diagnosis, while the remaining third (37.5% and 35.3%) occurred after the tenth year, confirming that both arterial and venous episodes were relatively early manifestations of SLE (47).

Some thrombosis risk factors, such as smoking and dyslipidaemia (47), were not included in this study. However, the presence or absence of these factors alone is unlikely to explain why patients with multiple genetic risk factors never had thrombosis, while others with no detectable predisposition to TE suffer from recurrent thrombotic events.

Table 4. Prevalence and relative risk values with 95% confidence intervals for each thrombophilia risk factor in the SLE population studied.

Risk factor	Group with thrombosis (n=22) n (%)	Group without thrombosis (n=83) n (%)	RR (95% CI)*
Lupus anticoagulant	16 (72.7)	21 (25.3)	4.90 (2.10–11.45)
Anti-phospholipid antibodies by ELISA	15 (68.2)	17 (20.5)	4.89 (2.21–10.83)
Factor V Leiden mutation	4 (18.2)	6 (7.2)	2.11 (0.89–5.02), ns
Factor II G20210A mutation	1 (4.5)	1 (1.2)	2.45 (0.58–10.33), ns
Elevated levels of factor VIII and vWF	4 (18.2)	6 (7.2)	2.11 (0.89–5.02), ns
Elevated level of homocysteine	6 (27.3)	14 (16.9)	1.59 (0.71–3.55), ns
Antithrombin deficiency	0	1	–
Decreased level of protein C	0	1	–
Decreased level of protein S	0	1	–
No risk factors detected	1 (4.5)	35 (42.2)	0.09 (0.01–0.65)

SLE, systemic lupus erythematosus; RR, relative risk; CI, confidence interval; ns, not significant; ELISA, enzyme-linked immunosorbent assay; vWF, von Willebrand factor. *RR within the whole SLE group.

Our work has some important limitations. It is a retrospective, single-centre analysis in a patient population followed at a national referral centre. This may introduce an element of referral bias. The nature of our study also limited the number of patients available. This is probably the reason for our failure to find a statistically significant effect for several parameters well known to carry a moderate thrombosis risk in the general population. Furthermore, as for any longitudinal study, controlling for fluctuations in the measured parameters is difficult. However, the inclusion of a complete set of laboratory parameters that are known thrombotic risk factors in the general population, and their comparison to the aPL in a relatively uniform SLE patient population, makes our study valuable.

In summary, we conclude that the presence of aPL carries a high TE risk in SLE. Other well-known TE risk factors also contribute to the thrombotic risk, although higher numbers would be needed to statistically prove this tendency. Thus, while testing for aPL clearly has clinical value, routine screening for the other parameters examined does not seem warranted.

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