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REGULAR ARTICLE

Clinical significance of anti-protein Z antibodies in patients with lupus anticoagulant☆

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Abstract

Introduction: Protein Z serves as cofactor for the inactivation of factor Xa by the plasma protein Z-dependent protease inhibitor. Deficiency of protein Z was reported to exhibit a clinical manifestation like lupus anticoagulant characterised by thrombosis and fetal loss. As anti-protein Z antibodies may be associated with low protein Z levels, we hypothesised that anti-protein Z antibodies might play a role in lupus anticoagulant (LA).
Materials and methods: Anti-protein Z antibodies were measured by commercially available ELISA in 102 LA-patients (69 with and 33 without thrombosis) and 33 healthy volunteers.
Results: Elevated anti-protein Z IgG and/or IgM, IgG and IgM antibody levels were more prevalent among LA-patients (62%, 35%, 45%) than among controls (50%, 25%, 25%), but the difference was only statistically significant for the IgM subtype ($p=0.037$). Anti-protein Z IgG (odds ratio [OR] 0.77, 95% confidence interval [CI] 0.33–1.82) and IgM (OR 0.82, CI 0.35–1.88) antibody levels in the highest quartile of controls did not indicate an increased risk for thrombosis among LA-patients. Anti-protein Z IgG (OR 2.0, CI 0.5–7.6) and IgM (OR 1.8, CI 0.5–6.6) antibody levels in the highest quartile of controls were more prevalent in women with pregnancy loss than in those with normal pregnancy, but the difference was not statistically significant.
Conclusion: Our data indicate that anti-protein Z antibodies are not associated with thrombosis in LA. However, women with LA and pregnancy loss show a tendency towards elevated anti-protein Z antibody levels.

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Introduction

Protein Z is a vitamin K dependent plasma glycoprotein that has structural homology to other vitamin K dependent plasma glycoproteins of coagulation including factor VII, IX, X, protein C and protein S, but in contrast to these serine protease zymogenes it lacks the proteolytic function. However, protein Z serves as cofactor for the inhibition of activated factor X by forming a calcium-dependent complex with protein Z-dependent protease inhibitor at the phospholipid surface and thereby hampers the coagulation cascade. Apart from its anticoagulant function, protein Z enhances the binding of thrombin to the phospholipid surface, which may promote thrombus formation [1]. In one study low levels of protein Z have been found in patients with bleeding of unknown origin [2], but two other studies failed to detect an association between protein Z and a bleeding tendency [3,4]. In contrast, an increasing body of evidence suggests that deficiency of protein Z leads to a propensity for thrombosis. Recently, low plasma levels of protein Z were found to be associated with an increased risk for venous thrombosis [5]. Moreover, clinical data show that protein Z deficiency is implicated in acute coronary syndrome [6] and ischemic stroke [7,8]. Interestingly, it has been demonstrated that protein Z deficiency dramatically increases the severity of the prothrombotic phenotype of factor V Leiden in mice [9]. In accordance with this finding, patients with factor V Leiden und low protein Z levels had a higher frequency and earlier onset of thromboembolic complications than patients with factor V Leiden and normal protein Z levels [10].

Lupus anticoagulant (LA) includes a heterogeneous group of autoantibodies primarily directed against certain plasma proteins such as beta-2-glycoprotein I and prothrombin and is clinically characterised by venous and arterial thrombosis as well as fetal loss. The mechanism of thrombosis has not been completely clarified in LA up to the present. Recent investigations were focused on testing the clinical significance of antiphospholipid antibodies possessing LA activity to identify patients with an increased risk for thrombosis and fetal loss. Only anti-beta2-glycoprotein antibodies were found to be a reliable marker of both thrombosis and fetal loss [11,12]. Anti-protein Z antibodies are also commonly present in LA and there might be a correlation between anti-protein Z antibody levels and protein Z levels [13]. As protein Z deficiency is associated with thrombosis and pregnancy loss, it may be hypothesised that anti-protein Z antibodies are involved in the clinical manifestation of LA. Therefore we investigated whether anti-protein Z antibodies are associated with thrombosis and pregnancy loss in patients with persistent LA.

Patients and methods

A total of 122 patients with a previously diagnosed persistent LA known to our hemostasis outpatient department of the Medical University of Vienna was recruited for further investigation between May 2001 and October 2004. The study was approved by the local Ethics Committee. After participants had given their written informed consent to this investigation, patients' medical history was recorded by means of a standard

Table 1 Demographic data of the study population; values are given as median and interquartile range

	LA with thrombosis	LA without thrombosis	Healthy controls
No. of patients	69	33	33
Sex (women/men)	57/12	26/7	25/8
Age at study entry, years	41.1 (31.0–60.1)	58.2 (38.7–67.3)	44.9 (38.6–56.4)
Current smokers	20 (29%)	13 (39%)	9 (27%)
Oral contraceptives or hormone intake	5/57 (9%)	1/26 (4%)	5/25 (20%)
No. SLE	8	3	0
No. incomplete SLE	10	7	0
F V: R506Q mutation	5	1	4
F II: G20210A mutation	3	0	2
Elevated F VIII level	7	3	1
Antithrombin deficiency	1	0	0
Hyperhomocysteinemia	14	9	4

Abbreviations: SLE — systemic lupus erythematosus.
Note: None of the patients had protein S or protein C deficiency; one patient with thrombosis had an autoimmune disease characterised by autoimmune hepatitis, autoimmune thyreoditis, vasculitis and Sjögren Syndrome; one patient without thrombosis had rheumatoid arthritis.