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Antiphospholipid antibodies in patients with upper-extremity deep vein thrombosis

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Abstract

The levels of antibodies to cardiolipin and β2-glycoprotein I and polymorphic variants G1691A of Factor V (factor V Leiden, FVL) and G20210A of prothrombin gene (G20210A) were studied in 16 patients with upper-extremity deep vein thrombosis (UEDVT). Most of patients with this syndrome have elevated values of these antibodies. Two of these patients are heterozygous carriers for G20210A and 1 – for FVL. Three patients with UEDVT and systemic lupus erythematosus (SLE) are positive for ANA and two others (one of them with Raynaud syndrome) have border line titre 1 : 80 for ANA. All 3 patients with SLE are women and the interval between the development of the UEDVT and the onset of SLE was 1-4 years. We would like to suggest that: 1) UEDVT could be the first clinical symptom of Antiphospholipid syndrome, and 2) UEDVT may be the first clinical manifestation of SLE preceding the development of the systemic autoimmune disease by several years.

Key words: *SLE, antiphospholipid antibodies, upper-extremity deep vein thrombosis.*

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Introduction

Upper-extremity deep vein thrombosis (UEDVT) accounts for approximately 10% of all cases of deep vein thrombosis (DVT) [1]. Usually the axillar vein and the subclavian vein are involved. According to the mechanism of thrombosis, UEDVT is classified as primary and secondary. Primary UEDVT includes the following disease entities: Paget-Schroetter syndrome (effort thrombosis), thoracic outlet syndrome (TOS) and cases of idiopathic UEDVT. In the 19th century, Sir James Paget (1814-1899) and Leopold von Schroetter (1837-1908) described venous obstruction in the upper extremity, which in 1949, Hughes [2] called Paget-Schroetter syndrome (thrombosis of the axillary – subclavian vein). Paget-Schroetter syndrome is also known as "effort-induced thrombosis", because it is frequently associated with an extreme physical effort [3] in young males who are involved in active sport games, such as long-distance swimming, wrestling, handball, baseball, badminton, rowing, weight lifting or body building exercises. The proposed mechanism of thrombosis in these patients is intimal microtrauma of the vein with subsequent thrombus formation and vascular obstruction [4].

Another form of UEDVT is TOS, associated with thoracic outlet abnormalities and variations, such as abnormalities of the clavicular and cervical ribs, muscle hypertrophy and muscular fascial band, long transverse processes of the cervical spine compressing and damaging the adjacent veins.

Secondary UEVT is observed in oncological patients [5]. The increased risk of DVT in these patients is associated with the following factors: underlying neoplastic disease, advanced age, surgical intervention, hypercoagulability state, chemotherapy, prolonged bed rest, infections, central venous line, etc. Other causes of secondary UEDVT are surgical interventions in this area, pregnancy, and oral contraceptives. Some prothrombotic factors, such as factor V Leiden, prothrombin gene mutation (G20210A), hyperhomocysteinemia, antithrombin III, protein C and protein S deficiency have also been stated as causative and/or predisposing factors [6].

Aim of the study

The aims of our study were:

1. To investigate the serum concentration of the antibodies to cardiolipin (aCL) and to β_2-glycoprotein I (aB-2-GPI) in patients with UEDVT.
2. To evaluate the significance of some inherited factors for thromboses in these patients.
3. To search other diseases connected with UEDVT.

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Material and methods

Sixteen patients (13 females and 3 males, aged 6-53 years) with UEDVT and 30 controls (13 females and 17 males, aged 30-40 years) were investigated for the presence of aCL and aB-2-GPI (ELISA method, Orgentec-Germany), lupus anticoagulant (LA, using routine aPTT testing method); antinuclear antibodies (ANA, indirect immunofluorescent test on Hep-2 cells, Euroimmune) and polymorphic variants G1691A of factor V (Factor V Leiden, FVL) and G20210A of prothrombin genes (G20210A) with polymerase chain reaction (PCR). All antiphospholipid antibodies were investigated twice, at least 2 months apart. Antibodies that were detected twice as being above the normal limits were considered positive. The normal limits of the stated antiphospholipid antibody assays for the Bulgarian population were established investigating 50 healthy volunteers (cut off values: IgG aCL – 22 GPL; IgM aCL – 11 MPL; IgG β2GPI – 20 U/ml; IgM β2GPI – 10 U/ml). According to the classification criteria for the diagnosis of APS [7], only aCL > 40 U and β2GPI > 99-th percentile (Table 1) were considered positive.

The diagnosis of UEDVT was made using patients' history, physical evaluation, venography and Doppler-sonography. None of the studied patients had chronic infections, chronic renal or hepatic diseases. None of the female patients was taking oral contraceptives or hormone-replacement therapy, and none was pregnant. None of the investigated patients was an active sportsman, none had prolonged immobilization preceding the development of DVT, none had a malignant disease or central venous line. Several patients had underlying or accompanying diseases: 2 had systemic lupus erythematosus (SLE), 1 – had SLE and thrombosis of vena cava inferior, 2 had pulmonary embolism (PE), 1 had thrombosis of vena cava superior of no detectable cause, 1 had disseminated intravascular coagulation (DIC) of no apparent cause, 1 had Raynaud's syndrome.

Results

The upper limits of antiphospholipid antibodies were [7]: for IgG aCL – 40 GPL; for IgM aCL – 40 MPL [7]; for IgG aB-2-GPI – 20 U; for IgM aB-2-GPI – 11 U. In accordance with these threshold values, 9/16 (56%) patients had positive IgG aCL; 1/16 (6 %) – positive IgM aCL; 7/16 (44%) – positive IgG aB-2-GPI and 4/16 (25 %) – positive IgM aB-2-GPI. Overall 5/16 patients (31%) had no positive autoantibodies. Positive LA (using standard aPTT method) was detected in 4 patients – 25% (patients N 2, 3, 4, 6; in all in association with high antiphospholipid antibodies). Three patients with UEDVT and SLE (NN 1, 6, 10) had positive ANA and two others (one of them with Raynaud's syndrome) had border-line ANA titer of 1 : 80 (Table 1). Two patients (12 %) were heterozygous carriers of G20210A and 1 (6 %) – of FVL (Table 1).

Table 1. Patients with UEDVT

N	Gender	Age	Other diseases	ANA	IgG ACL	IgM ACL	IgG aB2GPI	IgM aB2GPI	Other
1	F	33	SLE, thrombosis of vena cava inferior	1:640	30	24	30	12	
2	F	30	DIC	Neg	54	17	12	12	
3	M	6	Thrombosis of vena cava superior	Neg	100	7	10	2	
4	F	38	_	Neg	100	5	38	4	
5	M	53	PE	Neg	14	3	10	8	G20210A
6	F	26	SLE	1:640	18	150	50	20	G20210A
7	F	38	_	Neg	36	8	4	2	
8	F	24	_	Neg	40	2	45	16	
9	F	30	PE	Neg	56	3	10	8	
10	F	40	SLE	1:160	63	8	80	20	
11	M	50	_	Neg	145	10	53	20	FVL
12	F	47	_	Neg	120	20	14	5	
13	F	42	_	Neg	2	24	2	2	
14	F	48	Raynaud's syndrome	1:80	42	7	44.8	5.5	
15	F	50	_	1:80	28	4	14	12	
16	F	40	_	Neg	3	2	5	6.2	

F – female; M – male; PE – pulmonary thromboembolism; SLE – systemic lupus erythematosus; ANA – antinuclear antibody; aCL – anticardiolipin antibody; aB2GPI – β-2-glycoprotein-I antibody; Neg – negative; G20210A – 20210 prothrombin gene mutation; FVL – factor V Leiden mutation

All 3 patients with SLE were women and the interval between the development of the UEDVT and the onset of SLE was 1 year (N 10), 2 years (N 6) and 4 years (N 1). Subsequently, two of them (N 1 and N 6) developed severe forms of SLE – lupus nephritis, and received high doses of corticosteroids, cyclophosphamide, intravenous immunoglobulins and low molecular weight heparins.

Discussion

Upper-extremity deep vein thrombosis is much rarer than the DVT of the lower extremities [8]. Along with the etiological factors stated above, several newer prothrombotic conditions have been described, including the antiphospholipid antibodies, FVL and G20210A gene mutation that are known to have a pathogenic role in UEDVT. According to some authors, antiphospholipid antibodies are found in a small proportion of UEDVT patients – between 3.7% [9] and 7% [10], whereas others describe a much higher prevalence – 14.8% [11], 22% [8] and 26.8% [12]. In our study, IgG aCL had the highest prevalence – 56% of the patients, and 6/16 (37%) had more than one positive antibody. Overall 11/16 (69%) patients with UEDVT without clinical data for effort – induced thrombosis, cancer, oral contraceptives, central venous lines or anatomical abnormalities had positive antiphospholipid antibodies.

Antibodies to cardiolipin are found in 17-86% of the SLE patients and are known to have a pathogenic role in the development of thrombotic complications in these patients [13]. DVT develops 0.5-21.5 years after the first manifestations of SLE, and in 50% of the SLE patients, these complications develop within the first 2.5 years after the diagnosis [14]. Subclavian vein thrombosis is rare in SLE patients. Brower *et al.* describe this complication in 2/44 patients in their series [14]. On the other hand, Cervera *et al.* [15] have found that only 1.9% of the APS (antiphospholipid syndrome) patients have subclavian vein thrombosis. It is of particular interest in our study that in three SLE patients, subclavian-axillary vein thrombosis was the first manifestation of lupus. All three patients had positive antiphospholipid antibodies and clinical data for the antiphospholipid syndrome. At the diagnosis of UEDVT, the levels of antiphospholipid antibodies were high, but ANA were not investigated. In the study of Chang *et al.* [16], the first manifestation of SLE in 18/426 (4.2%) patients was a venous thrombotic incident.

According to Rees *et al.* [17], the highest prevalence of FVL among Europeans is observed in Greeks – 15%. In our previous study, we have shown that the prevalence of FVL among healthy Bulgarians is very high – 11.5% and 9% of healthy persons are carriers of G20210A gene mutation [18]. The prevalence of heterozygous carrier genotype for FVL among UEDVT patients shows wide variations: 3.7% [11], 4.9% [12], 7.4% [9], 10.6% [8], 9% [10], as does the G20210A genotype – from 0% [8, 12] to 10% [10]. In our study, among idiopathic UEDVT patients, 1/16 (6%) was a heterozygous carrier of FVL and 2/16 (12%) – of G20210A. According to Afeltra *et al.* [19], in Italy 11% of the SLE patients are heterozygous carriers of G20210A and 3% – of FVL, whereas in Turkey, Topaloglu *et al.* [20] have found these mutations in 3.6% and 12.6%, respectively. Despite the high prevalence of FVL, these authors state that the development of thromboses in these patients is associated with multiple other factors, besides the genetic thrombophilia. In Hungary, Regéczy *et al.* [21] have found that 13% of the SLE patients are heterozygous carriers of FVL and in the carriers, the development of thromboses is more frequent. In France, Barcat *et al.* [22] have found G20210A in 2% of the SLE patients. In the Netherlands, FVL has been found in 7.9%, and G20210A – in 1.4% of the SLE patients [14]. According to our previous studies, 5% of the SLE patients are heterozygous carriers of FVL and this prevalence is lower than in the healthy Bulgarian population [23]. In two patients with UEDVT we found a combination of two prothrombotic factors – high antiphospholipid antibody levels plus G20210A in one SLE patient and high antiphospholipid antibody levels plus FVL in a UEDVT patient without SLE (Table 1).

An interesting overlap in our study was the association between acquired (positive antiphospholipid antibodies) and genetically determined (prothrombin gene mutation and FVL) thrombophilia. This suggests the need for investigation of genetic markers of an increased thrombotic risk in UEDVT patients.

In UEDVT patients, we found different accompanying diseases and conditions, other than SLE, namely thrombosis of vena cava inferior and vena cava superior, disseminated intravascular coagulation (DIC), and pulmonary thromboembolism (PE) as rare embolic complication. One patient had Raynaud's syndrome (Table 1).

The results of our study in a small cohort of idiopathic UEDVT show that the most important prothrombotic factor appears to be the antiphospholipid antibodies. New initiatives for the elucidation of the exact mechanism of thrombosis is APS and for the harmonization and standardization of the methods and are currently taking place around the world [24].

Yet, there remains a certain proportion of patients with idiopathic UEDVT in whom no detectable cause exists [25]. In our cohort, 4 patients (25%) had no detectable antiphospholipid antibodies or prothrombotic gene mutation (patients N7, 13, 15, 16 – Table 1).

Conclusions

Upper-extremity deep vein thrombosis is a disease with uncertain etiology. Most of our patients with this disorder had high levels of aCL and aB-2-GPI antibodies and a part of them subsequently developed other thrombotic incidents. Of great interest is the fact that 3 patients with

UEDVT subsequently developed SLE. We would like to suggest that: 1) UEDVT could be the first clinical symptom of the antiphospholipid syndrome, and 2) UEDVT may be the first clinical manifestation of SLE preceding the development of the systemic autoimmune disease by several years.

The authors declare no conflict of interest.

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