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THE FREQUENCIES OF FV LEIDEN AND FII G20210A MUTATIONS IN PATIENTS WITH DIFFERENT CLINICAL MANIFESTATIONS OF VENOUS THROMBOEMBOLISM: EXPERIENCE FROM LARGE SERBIAN COHORT

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Venous thromboembolism is a multifactorial disorder with two manifestations: deep-vein thrombosis and pulmonary embolism. Pulmonary embolism is usually considered as the complication of deep-vein thrombosis, but there are reported cases of isolated pulmonary embolism. FV Leiden and FII G20210A mutations are most common genetic risk factors for the venous thromboembolism. Several studies reported "FV Leiden paradox": lower prevalence of FV Leiden mutation among patients with isolated pulmonary embolism than among those with deep-vein thrombosis. The aim of this study was to determine FV Leiden and FII G20210A mutations frequency in thrombophilic patients in Serbian population. We tested prevalence of these mutations carriers in 1427 individuals divided in three groups of patients (with deep-vein thrombosis, deep-vein thrombosis/ pulmonary embolism and isolated pulmonary embolism) and control group. All subjects were tested for these mutations using PCR-RFLP analysis. Detected frequency of FV Leiden heterozygous carriers in patients with isolated pulmonary embolism was 6.9% (for FII G20210A 11.6%), while in other two groups of patients with deep-vein thrombosis and deep vein thrombosis/pulmonary embolism, frequency was 18.6% (for FII G20210A mutation were 11.6% and 8.3%, respectively). Our results showed that FV Leiden mutation is less frequent in patients with isolated pulmonary embolism than in patients with deep-vein thrombosis or deep-vein thrombosis accompanied with

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pulmonary embolism, confirming "FV Leiden paradox". On the other hand, detected frequency of FII G20210A mutation carriers was similar in all three groups of patients.

Keywords: deep-vein thrombosis; pulmonary embolism; venous thromboembolism; FII G20210A; FV Leiden; paradox

INTRODUCTION

Venous thromboembolism (VTE) is a common vascular disease with two clinical manifestations, deep-vein thrombosis (DVT) and pulmonary embolism (PE) (KROEGEL and REISSIG, 2003; NAESS *et al.*, 2007; VAN LANGEVELDE *et al.*, 2012). VTE causes significant morbidity and mortality, with an incidence of one to three per 1000 per year (NAESS *et al.*, 2007). Pulmonary embolism is usually considered as the complication of DVT, but there are reported cases of isolated PE (iPE) which do not occur as a consequence of DVT (CALDERA *et al.*, 2002; AR, 2012).

Risk factors for VTE have been extensively studied. This is a multifactorial disease with acquired and genetic risk factors interacting dynamically. The key acquired risk factors for VTE comprise trauma, surgery, immobilization, advanced age, pregnancy and malignity. The most common genetic risk factors are FV Leiden and FII G20210A mutations. FV Leiden (G1691A) mutations leads to Arg506Gln amino acid substitution which disrupts activated protein C cleavage cite (BERTINA *et al.*, 1994). Frequency of FV Leiden variant is 11% to 29% in patients with VTE (BERTINA *et al.*, 1994; RIDKER *et al.*, 1995; DJORDJEVIC *et al.*, 2004). Heterozygous carriers of this mutation have seven fold higher risk of VTE and homozygous carriers 80-fold higher risk compared to general population (KOSTER *et al.*, 1993). FII G20210A is located in 3‘UTR of prothrombin gene and leads to elevated protein level by increasing efficiency of mRNA processing (POORT *et al.*, 1996; BAUER *et al.*, 2000; DANCKWARDT *et al.*, 2004). The FII G20210A variant was found in 4% to 17% of patients with VTE and has been linked to a 1.3- to 8-fold increased risk for VTE (TOSETTO *et al.*, 1999; DJORDJEVIC *et al.*, 2004).

Several authors reported a lower prevalence of FV Leiden mutation among patients with iPE than among those with DVT-so called ,,FV Leiden paradox,, (GADELHA *et al.*, 2010; VAN LANGEVELDE *et al.*, 2012). Although this paradox has been shown repeatedly, the mechanism is still unclear. The similar findings were reported for FII G20210A mutation by some authors suggesting the possible existence of ``FII G20210A paradox`` (MARGAGLIONE *et al.*, 2000; FRIEDLINE *et al.*, 2001), but were not confirmed by others (MEYER *et al.*, 2001; MARTINELLI *et al.*, 2007; SCHULMAN, 2007; GADELHA *et al.*, 2010; KOVAC *et al.*, 2010).

The aim of this study was to determine the frequency of FV Leiden and FII G20210A mutations in patients with iPE, DVT accompanied by PE or DVT solely and healthy controls. This is the first study exploring, so called, the ``FV Leiden and FII G20210A paradoxes`` in a Serbian population.

MATERIALS AND METHODS

Subjects

Our study was designed as a retrospective case-control study. Group of patients were selected by searching the database of over 4400 patients referred from 2002-2014, to our Institute for thrombophilia testing. Including criteria was: objectively diagnosed at least one DVT and/or PE (Doppler ultrasound, lung perfusion scan and helical tomography/computerized tomography).

Patients with diabetes mellitus and malignancy were not taken into account. Also, patients with combined thrombotic disorders, which in addition to DVT and/or PE, were suffered from myocardial infarction, stroke, arterial thrombosis or pregnancy loss, were excluded. Finally total of 1151 patients divided into three groups were included in the study: 189 patients with iPE (iPE group), 172 patients with DVT complicated with PE (DVT/PE group) and 790 patients with DVT only (DVT group). The control group encompassed 276 healthy subjects with no history of thrombotic events from the same geographic area of Serbia. Basic demographic characteristics of study groups are shown in Table 1. The study was approved by the local research ethics committee.

Table 1. Demographic characteristics of the patients and control groups

	number of subjects	sex m/f	age mean±SD	number of subjects with recurrent thrombotic events
control group	276	105/171	38±11.60	0
iPE group	189	96/93	43±14.18	19
DVT/PE group	172	101/71	43±13.39	164
DVT group	790	351/439	37±12.85	129

m-male, f-female, SD- standard deviation, iPE- isolated pulmonary embolism, DVT/PE-deep venous thrombosis accompanied with pulmonary embolism, DVT- deep venous thrombosis

Methods

Blood samples

Blood samples from all subjects were taken on 3.8% sodium citrate as anticoagulant. Genomic DNA was purified from whole blood using the QIAamp DNA Blood MiniKit (QIAGEN, Germany) according to manufacturer's standard protocol. DNA samples were stored at -20°C for further usage.

PCR-RFLP analysis

All subjects were tested for FV Leiden and FII G20210A mutations using PCR-RFLP analysis as previously described (DJORDJEVIC, 2001). The PCR products for FV Leiden mutation detection (generated by primers: 5'TGCCCAGTGCTTAACAAGACC3' and 5'TGTTATCACACTGGTGCTAA3') were digested by Mn*LI* (NE BioLabs, USA) restriction enzyme. The PCR products for FII G20210A mutation detection (generated by primers: 5'TCTAGAAACAGTTGCCTGGC3' and 5'ATAGCACTGGGAGCATTGAAGC3') were digested by Hind*III* (NE BioLabs, USA) restriction enzyme. Non mutated and mutated alleles were distinguished by the size of the restriction fragments, using electrophoresis on 10% polyacrylamide gels and visualised by silver staining.

Statistical analysis

Statistical methods used in this study: SD and median - for data distribution; Fisher's exact test - for comparation of FV Leiden and FII G20210A mutation prevalence between patients and controls; the odds ratio (OR) and 95% confidence interval (CI) - for risk assessment. The χ^2-test - for determination of the genotypes distributions deviations from Hardy-Weinberg equilibrium. Value P less than 0.05 was considered as statistically significant. Statistical analysis was performed by using Statistical Package for Social Sciences 13.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

RESULTS

For tested mutations, it has been shown that all patients' groups and control group were in Hardy-Weinberg equilibrium using the χ^2 test.

In controls, the 24 out of 276 tested subjects (2.1%) were carriers of FV Leiden or FII G20210A mutations, while in patients 317 out of 1151 tested subjects (27.5%) were carriers of any of these two mutations (Table 2) and 16 patients were carriers of both mutations (1.4%).

Table 2. Genotype frequencies of FV Leiden and FII G20210A mutations in patient groups and controls

		Control group (n=276)	iPE group (n=189)			DVT/PE group (n=172)			DVT group (n=790)		
		n (%)	n (%)	OR [a] 95%CI[a]	P [a]	n (%)	OR [b] 95%CI[b]	P [b]	n (%)	OR [c] 95%CI[c]	P [c]
FV Leiden	Heterozygous	13 (4.7)	13 (6.9)	1.49 0.68-3.30	.320	32 (18.6)	4.62 2.35-9.10	<.0001	147 (18.6)	4.62 2.58-8.30	<.001
	Homozygous	1 (0.4)	1 (0.5)	1.46 0.09-3.53	.790	5 (2.9)	8.23 0.95-71.09	.060	11 (14.0)	3.88 0.50-0.21	.020
FII G20210A	Heterozygous	10 (3.6)	22 (11.6)	3.50 1.62-7.58	.002	20 (11.6)	3.50 1.60-7.67	.002	66 (8.3)	2.43 1.23-4.78	.010
	Homozygous	0	0	-	-	0	-	-	2 (0.2)	1.75 0.08-6.64	.720

[a] iPE patient group *vs.* control group was tested,

[b] DVT/PE patient group *vs.* control group was tested,

[c] DVT patient group *vs.* control group was tested

In comparison to control group the FV Leiden heterozygous carriers frequency was significantly increased in patients with DVT/PE and in patients with DVT solely (P<0.0001), but this was not the case with patients suffered from iPE (P=0.320) (Table 2).

We detected significantly higher frequency of heterozygous carriers of FII G20210A mutation in all three groups of patients (iPE, DVT/PE and DVT) in comparison to control group (Table 2).

The FV Leiden heterozygous carriers showed higher risk to develop DVT or DVT/PE than iPE ((OR=2.48; 95%CI 1.44-4.26) and (OR=2.47; 95%CI 1.30-4.39), respectively), while there were similar increase in the prothrombic risk for FII G20210A mutation carriers in all three groups of patients (Table 3).

Table 3. Genotype frequencies of FV Leiden and FII G20210A mutations in iPE group vs. DVT and DVT/PE patient groups

	DVT vs iPE		DVT/PE vs iPE	
	OR 95%CI	P	OR 95%CI	P
FV Leiden heterozygous	2.48 1.44-4.26	0.001	2.47 1.30-4.39	0.006
FII G20210A heterozygous	1.00 0.52-1.90	0.997	0.69 0.41-1.15	0.158

iPE- isolated pulmonary embolism, DVT/PE-deep venous thrombosis accompanied with pulmonary embolism, DVT-deep venous thrombosis

DISCUSSION

Results of our study showed that FV Leiden carriers had statistically significant increased risk for developing DVT (OR=4.62, 95%CI 2.35-9.10) or DVT accompanied by PE (OR=4.62, 95%CI 2.58-8.30), but not for iPE (OR=1.49, 95% 0.68-3.30). These findings are in concordance with the results of the previous studies (MARTINELLI *et al.*, 2007; SCHULMAN, 2007; KOVAC *et al.*, 2010; VAN LANGEVELDE *et al.*, 2012) and confirm existence of the "FV Leiden paradox" in Serbian population.

Some findings could give a possible explanation of stronger association of FV Leiden mutation with DVT than PE. FV Leiden can affect the structure of the thrombus by making it more stable and adherent to the vessel wall, so the chance of embolization is decreased (BJÖRGELL *et al.*, 2000; PERRIER, 2000; FAVALORO, 2008). Also, PE occurs more frequently as a consequence of the thrombus formation in the proximal veins, which was found to be less often affected in the FV Leiden carriers 28. However, further studies are required to establish the exact mechanism involved in this ,,paradox,,.

Regarding FII G20210A mutation, some studies reported higher risk for DVT than for PE, but this ,,FII paradox,, was not confirmed by others authors (MARGAGLIONE *et al.*, 2000; FRIEDLINE *et al.*, 2001; MEYER *et al.*, 2001; MARTINELLI *et al.*, 2007; SCHULMAN, 2007; GADELHA *et al.*, 2010; KOVAC *et al.*, 2010). Several studies found no difference in the prevalence of FII G20210A mutation among groups of patients suffering from DVT or PE (DE MOERLOOSE *et al.*, 2000), or reported a lower frequency of FII G20210A mutation carriers in patients suffered from DVT than in PE patients (DE MOERLOOSE *et al.*, 2000; MEYER *et al.*, 2001; OKUMUS *et al.*, 2008; WEISCHER *et al.*, 2010). Results of our study showed that heterozygous carriers of FII G20210A mutation have increased risk in all three groups of patients (DVT, DVT/PE and iPE) compared to control group, aligning our study to those in which ,,FII paradox,, is not proved.

Recently, Pomero and coworkers in meta-study showed that both mutations, FV Leiden and FII G20210A are statistical significant risk factors for iPE (POMERO *et al.*, 2014). In this paper authors analyzed 18 studies including in total 1949 iPE patients tested for FV Leiden and 1611 iPE patients tested for FII G20210A mutation. However, these results should be interpreted with limitations that evaluated studies had different inclusion and exclusion criteria, and there are discrepancies of the analyzed group's sizes (large cohort of subjects are from one single study) (POMERO *et al.*, 2014).

Thought our study consists of 1427 subjects, its limitation refers to relatively small number of patients with iPE and DVT accompanied with PE in comparison to DVT group. The reason for this lies in the fact that the DVT are more frequent than the other two events, pointing out that further studies should be done in larger cohort.

CONCLUSION

Results of our study showed that FV Leiden mutation is less frequent in patients with iPE than in patients with DVT or DVT accompanied by PE, confirming so called "FV Leiden paradox". On the other hand, there were no differences in frequencies of FII G20210A mutation carriers in all three groups of patients.

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UČESTALOST FV LEIDEN I FII G20210A MUTACIJA KOD PACIJENATA SA RAZLIČITIM KLINIČKIM MANIFESTACIJAMA VENSKOG TROMBOEMBOLIZMA: ISKUSTVA IZ VELIKE STUDIJE U SRPSKOJ POPULACIJI

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Izvod

Venski tromboembolizam je multifaktorijalno oboljenje sa dve kliničke manifestacije: tromboza dubokih vena i plućna embolija. Plućna embolija se obično smatra komplikacijom tromboza dubokih vena, ali postoje dokumentovani slučajevi izolovane plućne embolije. FV Leiden i FII G20210A mutacije su najčešći genetički faktor rizika za nastanak venskog tromboembolizma. Nekoliko studija je pokazalo takozvani "FV Leiden paradoks": nižu učestalost FV Leiden mutacije kod bolesnika sa izolovanom plućnom embolijom u odnosu na bolesnike sa dijagnostikovanom dubokom venskom trombozom. Cilj ovog istraživanja bio je da se utvrdi učestalost FV Leiden i FII G20210A mutacije kod bolesnika sa trombotičkim događajima u populaciji Srbije. Testirali smo učestalosti ove dve mutacije kod 1427 ispitanika podeljenih u tri grupe bolesnika (sa dubokom venskom trombozom, sa trombozom dubokih vena sa embolijom pluća i sa izolovanom plućnom embolijom) i kontrolnu grupu. Svi ispitanici su testirani na prisustvo ovih mutacija PCR-RFLP analizom. Utvrđena učestalost FV Leiden heterozigotnih nosilaca kod bolesnika sa izolovanom plućnom embolijom je bila 6,9% (za FII G20210A mutaciju 11,6%), dok je kod bolesnika sa dubokom venskom trombozom i kod bolesnika sa dubokom venskom trombozom praćenom plućnom embolijom ta učestalost iznosila 18,6% (za FII G20210A mutaciju 11,6% i 8,3%, respektivno). Rezultati naše studije su pokazali da je FV Leiden mutacija manje učestala kod bolesnika sa izolovanom plućnom embolijom nego kod bolesnika sa trombozom dubokih vena ili trombozom dubokih vena sa plućnom embolijom, što ide u prilog potvrdi "FV Leiden paradoksa". Sa druge strane, učestalosti FII G20210A mutacije su bile slične za sve tri ispitivane grupe bolesnika.

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