Applied Cardiopulmonary Pathophysiology 16: 32-36, 2012

Clinical significance of factor V G1691A- and prothrombin G20210A-mutations in cerebral infarction and patent foramen ovale

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Abstract

The clinical significance of inherited thrombophilia in the pathogenesis of cerebral infarction associated with patent foramen ovale (PFO) is estimated in a different way according to recent reports. Therefore, 92 patients suffering from ischemic stroke, among them either 46 subjects with or without PFO, were evaluated in an age- and gender-matched paired case-control study by genetically testing of factor V (FV) G1691A- and prothrombin (PT) G20210A-mutations. Patients with PFO had 19/46 (41.3%) FV- and 3/46 (6.5%) PT-mutations, whereas in patients without PFO only 9/46 (19.6%) FV- and 1/46 (2.2%) PT-mutations were observed. The prevalence of FV-mutations in PFO-patients was significantly higher (OR: 3.12, 95%CI: 1.11-8.95%) compared with patients not having PFO. PT-mutations were more frequently but not significantly associated with PFO. We conclude from these data that FV G1691A-mutations combined with PFO play a significant role in the pathogenesis of cerebral infarction. Since FV-mutation, on the other side, is a particular risk factor of venous thrombosis, paradoxical embolism seems to be essential for the occurrence of stroke in association with PFO.

Key words: stroke, foramen ovale, thrombophilia

Introduction

Patent foramen ovale (PFO) which is a frequent finding in the general population has been revealed to be an independant risk factor for cerebral infarction [1, 2]. Apart from intraatrial thrombus formations the development of paradoxical embolism arising from the peripheral venous system is obviously essential for the occurence of stroke [3, 4]. In this context inherited thrombophilia predisposing for venous thrombosis might support the development of stroke in association with patent foramen ovale.

Various studies classified prothrombotic markers to a different extent as risk factors for stroke [5, 6]. However, only few reports partially showing controversial results are available addressing the role of thrombophilia in foramen ovale for the development of cerebral ischemia [7].

We therefore, by detecting factor V Leiden- and prothrombin G20210A-mutations as the most frequent thrombophilic markers, conducted an age- and sex-matched paired case-control study comparing patients suffering from cerebral infarction with and without PFO. The purpose of this investigation was to evaluate whether there might be a difference,

related to PFO, in the prevalence of those markers.

Patients and methods

Adult patients consecutively referred to our out-patient department for thrombophilia testing who had suffered one or more events of cerebral infarction were enrolled in this study. Cerebral infarction had to be confirmed by computed brain tomography or magnetic resonance imaging. PFO had to be ascertained by either transesophageal echocardiography (TEE) and/or transcranial doppler (TCD). On the basis of a case-control study with matched pairs each stroke patient with PFO was consecutively assigned to a stroke patient without PFO of same sex and equivalent age (range: +/-10%) at the first event of cerebral ischemia. Laboratory analysis of factor V (Leiden) G1691A- and prothrombin G20210A-mutations were performed by using a multiplex allele-specific polymerase chain reaction assay (Thrombo Type plus, HAIN LifeScience, Nehren (Germany)). Statistical analysis was performed by using Chi-square-testing and Fisher's exact test. A value of $p<0.05$ was considered significant.

Results

A total of 92 patients with ischemic stroke were enclosed into the study including 46 individuals each with and 46 without patent foramen ovale. PFO- and non-PFO-patients have been matched by pairwise sex- and age-related assignment. The demographic data and the results of genotyping looking at factor V G1691A- (Leiden-type) and prothrombin G20210A-mutations are listed in table 1. The frequency of factor V Leiden was significantly higher (more than 2-fold) in PFO-patients than in subjects without PFO (s. table 1 and fig. 1). Prothrombin mutation in PFO-patients was observed in 3 versus 1 case(s). This difference, however, was not significant. The occurrence of each genotype added up was significantly more frequent in the PFO-group (s. Table 1 and figure 1). All cases showed heterozygous genotypes. A combined presence of factor V Leiden and prothrombin mu-

Table 1: Demographic data and factor V and prothrombin genotypes in stroke patients with and without patent foramen ovale

	Stroke with patent foramen ovale	**Stroke without patent foramen ovale**	**Odds Ratio (95% Confidence interval) p Value**
Number (N)	46	46	
Sex (females/males)	31/15	31/15	
Age (range (years))	22-66	20-66	
Age (mean+/-SD))	42.8 ± 9.9	43.1 ± 9.6	
Factor V G1691A-mutation	19/46 (41.3%)	9/46 (19.57%)	2.89 (1.04-8.22) p = 0.0224
Prothrombin G20210A-mutation	3/46 (6.52%)	1/46 (2.17%)	3.13 (0.273-80.274) p = 0.617
Factor V + prothrombin mutations	21/46 (47.82%)	10/46 (21.74%)	3.02 (1.12-8.34) p = 0.0154

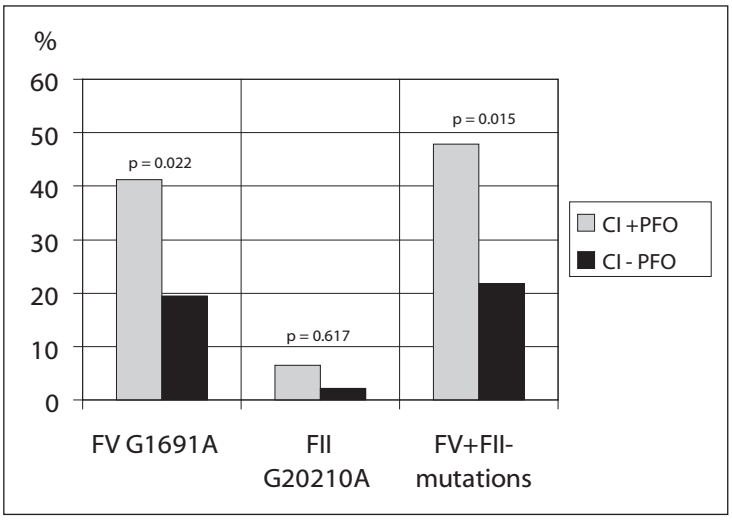

Figure 1: Frequency of factor V G1691A- and prothrombin G20210A-mutations in patients with cerebral infarction (CI) with (+PFO; n=46) and without patent foramen ovale (-PFO, n=46), p: p values for inter-group comparison

tation was not observed at all in any of the cases.

Discussion

The prevalence of PFO in the general population is reported to be between 15% and 35% [8-10]. Its role as a risk factor for the development of cerebral infarction has been established by studies of stroke-patients. However, this risk appears to be rather low in stroke-free subjects with PFO who were followed-up prospectively [10]. Therefore, it is assumed that additional risk factors might be responsible for increasing the likelihood of developing cerebral infarction. Since paradoxical embolization is claimed to be an essential factor in the pathogenesis of PFO-related stroke, prothrombotic mechanisms promoting the generation of thrombosis in the peripheral venous system might be considered as an accessory risk [3, 5, 6]. In this context inherited thrombophilia is obviously capable of increasing the probability of PFO-related stroke. Factor V Leiden genotype and prothrombin G20210A variant are the most common thrombophilic markers closely related with venous thromboembolism [11].

The results of our study showed indeed, as expected, a clear association between factor V Leiden mutation and PFO-related cerebral ischemia, approximately twice as much occurring among the cases of the PFO-group, which was significantly different compared with non-PFO-patients. The prothrombin mutation, as well, showed a markedly but not significantly higher prevalence in the PFO-group. These findings supply evidence that thrombophilic parameters like factor V Leiden and, to a lesser extent, prothrombin G20210A mutation have to be considered as a clinically relevant accessory risk of ischemic stroke in patients with PFO. Due to the close relationship of these markers with the formation of venous thrombosis, our data provide further evidence that paradoxical embolism is obviously an essential mechanism for developing stroke in PFO-patients.

Our findings do not clearly confirm the results of other reports on the relationship between thrombophilia and stroke. The majority of studies evaluating inherited thrombophilia in unselected stroke patients did not find a clear difference between patients and controls [5, 12, 13]. This is not necessarily contradictory to our findings, since PFO-patients have been selectively addressed in our study and comparison with healthy controls was not a decisive question. Corresponding data, however, are different among the reports on studies investigating thrombophilia

in patients with PFO [7, 14-18]. No clear evidence of a significant difference comparing healthy controls versus patients with PFO was shown as reported by some authors [17,19]. By contrast, significant differences in favour of prothrombin mutations and a marked trend for factor V Leiden among PFO-carriers compared with controls and non-PFO-patients have been observed by other authors [7, 14, 15, 17]. Accordingly, the prothrombin G20210A-mutation and, to a lesser extent, the factor V G1691A-mutation are claimed by these authors to be representative risk factors for PFO-related cerebral infarcts [7, 16].

These findings partly agree with our data. However, factor V Leiden, according to our results, is regarded as a stronger risk factor in PFO. These differences including the higher prevalence of thrombophilia in our populations, as well, are ascribed to a divergent design of our study, compared with the literature, which is based on a strictly matching by pairs for age and gender. Furthermore, preselection, to a certain extent, for thrombophilia testing might be a limitation of our study which, however, is largely eliminated by using similarly preselected patient-group as controls. Another issue refers to the geographic and ethnic diversity of inherited thrombophilia among the populations studied according to the reports of the literature [20]. In this context, a population of Central Europe as detected in our study is not necessarily comparable with patients of Southern Europe [16-18] or other regions or continents [12,14].

We conclude from our data, that the occurrence of factor V Leiden and, to a lesser extent, of prothrombin G20210A-mutation is a clinically relevant risk for the development of cerebral infarction in association with PFO. This relationship is obviously linked with paradoxical embolism possibly due to venous occlusive disease. Therefore, in the case of cerebral infarction, apart from neurological and cardiologic diagnosis, additional examinations of the peripheral venous system are recommended in patients with PFO and inherited thrombophilia. The results of these investigations should consistently be included into the preventive and therapeutic strategies.

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