Do common prothrombotic mutations influence the risk of cerebral ischaemia in patients with patent foramen ovale?

Systematic review and meta-analysis

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Summary

Conflicting results are available on the association of prothrombotic genetic abnormalities with patent foramen ovale (PFO)-related cerebral ischaemia. We comprehensively sought and identified studies of the association of both the factor V Leiden (FVG1691A mutation) and the prothrombin mutation (PT G20210A mutation) with PFO-related cerebral ischaemia and did meta-analyses to assess the evidence for such a relation. We analysed data from six eligible studies in 856 cases and 1,001 control subjects. Additional unpublished data from a new series including 463 subjects were also entered into the analysis. The PTG20210A variant was significantly associated with PFO-related stroke in comparison with both control subjects (odds ratio [OR] 3.85; 95% confidence interval [CI] 2.22 to 6.66) and non-PFO-associated stroke patients (OR 2.31; 95% CI 1.20 to 4.43), whereas a trend toward an association was observed for the FVG1691A mutation (OR 1.18; 95% CI 0.73 to 1.90, compared to control subjects; OR 1.14; 95% CI 0.62 to 2.09, compared to non-PFO-associated stroke patients). The status of carrier of either the FVG1691A mutation or the PTG20210A variant was associated with a risk for stroke of 1.98 (95% CI 1.38 to 2.83) and 1.62 (95% CI 1.03 to 2.57), as compared to control subjects and non-PFO-associated stroke patients, respectively. Addition of common prothrombotic genetic variants to standard initial screening may contribute to stratifying PFO-associated stroke patients at different risk of ischaemic events and targeting secondary prevention strategies.

Keywords

Patent foramen ovale, prothrombotic disorders, young, stroke

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Introduction

Understanding the pathogenic basis of the relation between patent foramen ovale (PFO) and cerebral ischaemia is critical when considering whether the inter-atrial cardiac defect is the cause of the vascular event, and thus, in identifying those high-risk patients who may benefit from percutaneous transcatheter closure of their PFO. Recently, several reports have focused on the potential role of an underlying prothrombotic state in predisposing young PFO carriers to brain embolism. Screening for procoagulant disorders might have an impact on the stratification of risk of recurrent events in patients with stroke and PFO, and, at an individual level, might help clinicians in selecting the most appropriate treatment options in these cases (1, 2). However, the few studies attempting to assess the association of prothrombotic abnormalities with PFO-related stroke have provided conflicting results (3–8), making any recommendation on whether to screen for prothrombotic disorders in these patients largely speculative. We therefore performed a systematic review and meta-analysis of the published literature regarding the association of the two
Figure 1: Forest plot of ORs and 95% CIs for ischaemic stroke associated with the PTG20210A variant (A), the FVG1691A mutation (B), or the status of carrier of either the FVG1691A mutation or the PTG20210A variant (C) in studies comparing PFO-related stroke cases and control subjects, and pooled summary OR and 95% CI estimate.
most common inherited thrombophilic disorders, factor V Leiden (FV<sub>G1691A</sub> mutation) and prothrombin G20210A (PT<sub>G20210A</sub> mutation) variant, with PFO-related stroke.

Methods

Search strategy

Computerised search of PUBMED (http://www4.ncbi.nlm.nih.gov/PubMed) was conducted until May 2008 to identify studies evaluating the relationship between inherited thrombophilia and PFO in the pathogenesis of ischaemic stroke. The search terms “patent foramen ovale”, “paradoxical embolism”, “cerebrovascular disorders”, “juvenile”, “thrombophilia”, “factor V Leiden”, “prothrombin”, and “APC resistance” were used. To screen for additional publications, we reviewed citations from retrieved articles. Both literature searches were limited to “human” and “English language”. We excluded studies in which only one of the two inherited prothrombotic conditions were analysed.

Additional data

Data from a new series of patients with first-ever premature ischaemic stroke consecutively admitted to the Department of Neurology, University of Brescia, Italy and the Department of Neurology, University of Heidelberg, Germany as well as from age- and sex-matched controls were entered into the meta-analysis (Pezzini-Lichy). Description of the methods and the standardised protocol for patients and controls’ documentation has been given elsewhere (3, 4).

Statistical analysis

Two separate meta-analyses were conducted: the first one comparing PFO-associated stroke patients and control subjects, the second one comparing PFO-associated and non-PFO-associated stroke patients. Meta-analyses were performed by Stata software (www.stata.com). Odds ratios (ORs) and 95% confidence intervals (CIs) were computed to summarise the results of each study. Heterogeneity testing of ORs was performed by DerSimonian-Laird method. Where homogeneity was present, the Mantel-Haenszel (M-H) summary OR (95% CI) was computed to pool the results; otherwise, a random effects model summary was applied.

Results

The search strategy retrieved six studies fulfilling the inclusion criteria, involving 856 ischaemic stroke cases and 1,001 non-stroke control subjects (3–8). The additional new series provided information on further 251 cases and 212 control subjects.

PFO+ versus control subjects

Data from 604 PFO-associated stroke cases and 1,213 control subjects were entered into the first meta-analysis. The pooled M-H estimate of the ORs for stroke was 3.85 (95% CI 2.22 to 6.66) associated with the PT<sub>G20210A</sub> variant, 1.18 (95% CI 0.73 to 1.90) associated to the FV<sub>G1691A</sub> mutation, and 1.98 (95% CI 1.38 to 2.83) associated with the status of carrier of either the FV<sub>G1691A</sub> mutation or the PT<sub>G20210A</sub> variant (Fig. 1).

PFO+ versus PFO-

Three out of the six studies involving 580 stroke cases were identified that satisfied inclusion criteria for the second meta-analysis (3–5). The additional new series provided information on further 251 patients. Thus, data from 374 PFO-associated stroke patients and 457 non-PFO-associated stroke patients were considered. The pooled estimate of risk for stroke was 2.31 (95% CI 1.29 to 4.33) associated with the PT<sub>G20210A</sub> variant, 1.14 (95% CI 0.62 to 2.09) associated with the FV<sub>G1691A</sub> mutation, and 1.62 (95% CI 1.03 to 2.57) associated with the status of carrier of either the FV<sub>G1691A</sub> mutation or the PT<sub>G20210A</sub> variant (Fig. 2).

Discussion

Although PFO is very common, not all PFOs are the same. The challenge for clinicians is to determine which PFOs confer an increased risk of stroke. Individuals with PFO can be subgrouped according to many characteristics (large vs. small PFO, provoked vs. unprovoked trans-septal gas passage, presence vs. absence of associated anatomical structures). However, which of these characteristics are clinically important in assessing the risk of embolic stroke is not entirely clear. The results of our meta-analysis support the assumption that an underlying hypercoagulable state may be a predisposing condition for PFO-related cerebral infarcts and might be used as a further criterion for risk stratification among subjects with PFO. This would appear to indirectly support the findings of sparse previous studies investigating the role of other inherited or acquired prothrombotic conditions in PFO-related cerebral ischaemia (3). The lack of association between FV<sub>G1691A</sub> mutation, the strongest predictor of venous thromboembolism, and PFO-related cerebral infarcts may appear unexpected, when assuming paradoxical embolism as the most likely mechanism of ischaemia in these cases. However, besides paradoxical embolism, other pathogenic processes, including embolisation from thrombi formed within the atrial septum (9, 10), and transient atrial arrhythmias (11), have been implicated in the occurrence of PFO-related cerebral ischaemia, and it is well-known that the hypercoagulable state associated with each of the two mutations may lead to genotype-specific clinical manifestations (12). It might be that the magnitude of the predisposing effect of each genotype may vary according to the specific mechanism of PFO-related cerebral ischaemia.

Study limitations

First, because of the relatively small number of subjects included in each study, publication bias (13) cannot be ruled out. Second, none of the studies included in the meta-analysis were population-based, which implies a potential bias in the selection of control subjects. Reliable answers for the association under investigation will only come from studies an order of magnitude larger than those performed to date, with appropriate selection of controls, which is only likely to be achieved with a multicenter collaborative approach. Although these limitations are noteworthy, the homogeneity of results of the studies, especially with respect to the association of the PT<sub>G20210A</sub> variant with PFO-related infarcts, is an argument against such potential drawbacks. Other methodological characteristics of the studies, including blinding of genotyping staff and genotyping method (genotyp-
Figure 2: Forest plot of ORs and 95% CIs for ischaemic stroke associated with the PTG20210A variant (A), the FVG1691A mutation (B), or the status of carrier of either the FVG1691A mutation or the PTG20210A variant (C) in studies comparing PFO-associated and non-PFO-associated stroke cases, and pooled summary OR and 95% CI estimate.
ing errors), misclassification (phenotyping errors), and inappropriate statistical methods, seem to have less influence on the detected associations.

**Conclusions**

Within the population of patients with PFO different mechanisms are probably operant which may be responsible for embolic events. Coagulation abnormalities appear to be major determinants in this regard. The results of our meta-analysis support the assumption that addition of common prothrombotic genetic variants to standard initial screening may generate a more effective method for stratifying PFO-associated stroke patients at different risk of ischaemic events. The assessment of these genotypes may thus contribute to the identification of those PFO-associated patients who might benefit from new strategies of secondary prevention.

**References**