Determinants of premature familial arterial thrombosis in patients with juvenile ischaemic stroke

The Italian Project on Stroke in Young Adults (IPSYS)

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Summary

Factors predicting family history (FH) of premature arterial thrombosis in young patients with ischaemic stroke (IS) have not been extensively investigated, and whether they might influence the risk of post-stroke recurrence is still unknown. In the present study we analysed 1,881 consecutive first-ever IS patients aged 18–45 years recruited from January 2000 to January 2012 as part of the Italian Project on Stroke in Young Adults (IPSYS). FH of premature arterial thrombosis was any thrombotic event [IS, myocardial infarction or other arterial events event] <45 years in proband's first-degree relatives. Compared with patients without FH of premature arterial thrombosis, those with FH (n = 85) were more often smokers (odds ratio [OR], 1.94; 95 % confidence interval [CI], 1.21–3.09) and carriers of procoagulant abnormalities (OR, 3.66; 95 % CI, 2.21–6.06). Smoking (OR, 2.48; 95 % CI, 1.20–5.15), the A1691 mutation in factor V gene (OR, 3.64; 95 % CI, 1.31–10.10), and the A20210 mutation in the prothrombin gene (OR, 8.40; 95 % CI 3.35–21.05) were associated with FH of premature stroke (n = 33), while circulating anti-phospholipids to FH of premature myocardial infarction (n = 45; OR, 3.48; 95 % CI, 1.61–7.51). Mean follow-up time was 46.6 ± 38.6 months. Recurrent events occurred more frequently in the subgroup of patients with FH of premature stroke [19.4 %); p = 0.051] compared to patients without such a FH. In conclusion, young IS patients with FH of premature arterial thrombosis exhibit a distinct risk-factor profile, an underlying procoagulant state and have worse vascular prognosis than those with no FH of juvenile thrombotic events.

Keywords

Stroke in young adults, cohort studies, risk factors in epidemiology

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Introduction

Over the last 50 years, a number of epidemiologic studies have clearly established that, regardless of the geographic location, a family history (FH) of arterial thrombosis increases the risk of ischaemic stroke (IS) (1, 2). Although the underlying biologic processes linking the two conditions have been also increasingly investigated, the mechanisms by which a FH of thrombosis might predispose to brain ischaemia is still an understudied area. Whether there are any specific conditions more likely playing a role remains, therefore, to be determined. The hypothesis of shared genes, shared environment, including common lifestyles and behaviours, or a combination of both has been repeatedly advocated and it is now accepted by most investigators, with no demonstration, however, of any pathogenic pathways and no factor consistently associated to the increased propensity to ischaemia in familial groups. Understanding these mechanisms implicates the potential of targeting specific and more aggressive preventive approaches to selected patients' groups and medical surveillance for at-risk relatives.

Studies conducted so far have observed that the propensity to familial aggregation of ischaemic disease may vary on the basis of the age of the probands, being higher among younger individuals (1, 3–7). This appears plausible when considering that the influence of non-familial, environmental, susceptibility factors increases with ageing. In this regard, inherited prothrombotic abnormalities have long been regarded as potential predisposing conditions, although a causal association between abnormalities of the haemostatic system and arterial ischaemic disease has never been definitively established (8, 9). Younger patients represent, therefore, the ideal target population to explore the pathogenic link between FH of arterial thrombosis and IS. In the absence of previous systematic studies or data from large cohorts of patients with juvenile stroke, we investigated what factors predict FH of premature arterial thrombosis in the setting of the Italian Project on Stroke at Young Age (IPSYS), and tested the hypothesis that these factors might also influence the risk of post-stroke recurrence in patients with familial aggregation of ischaemic disease.

Subjects and methods

Patients and study design

The IPSYS is a countrywide network of neurological centers with special interest in cerebral ischaemia at young age across Italy, aimed at recruiting patients with first-ever acute stroke who fulfill the following criteria: 1) age 18 to 45 years, and 2) CT- or MRI-proven cerebral infarction, in the setting of a hospital-based, multicentre, observational study. Criteria for patient selection, risk factor definition, diagnostic procedures and outcome assessment have been previously described (10, 11). Centers are included in the network provided that the recruitment process of stroke cases takes place prospectively. The study was approved by the local Ethics Committee. Informed consent was provided by all study participants. For the purpose of the present analysis, we screened data sets from patients consecutively admitted to 22 hospitals. The recruitment period was January 2000 through January 2012, and follow-up was completed January 2013. Stroke was defined as a sudden loss of global or focal cerebral function that persisted for >24 hours (h) with a probable vascular cause. IS due to sinus venous thrombosis, vasospasm after subarachnoid haemorrhage, cardiac surgery, occurring as an immediate consequence of trauma, and iatrogenic strokes were excluded. Acute phase therapy as well as long-term antithrombotic therapy and other treatment for secondary prevention were administered to all patients in accordance with published guidelines (12).

Family history

We obtained information on stroke and myocardial infarction events in first-degree relatives by interviewing probands and/or their close relatives. A positive FH of arterial thrombosis was defined as having a history of stroke or myocardial infarction in at least one first-degree relative (parents and siblings). Because the influence of FH of arterial thrombosis on stroke risk is expected to be higher when proband's family members are affected at young age, for the present analysis we considered a FH of premature stroke, which was defined as stroke occurring in first-degree relatives aged <45 years. The same cut-off of age was used to define a FH of premature myocardial infarction. We decided to use these stringent age criteria in order to enrich our cohort for subjects with a strong familial predisposition for arterial thrombosis.

Genetic analyses

Genomic DNA was isolated in all subjects from –20 °C frozen samples of EDTA anticoagulated whole blood using a standard DNA extraction. The G1691A mutation in the factor V gene (factor V Leiden) and the G20210A mutation in the prothrombin gene were determined according to a standardized multiplex polimerase chain reaction (PCR) method (13).

Outcome events

Only patients who survived the index event were entered into the present analysis. Death was considered due to the index stroke if it occurred within 30 days of symptoms onset. Subjects were included in the subgroup of patients who did not experience recurrence if they had at least a one-year follow-up. Follow-up evaluations were conducted at three months and then annually, and outcome events classified using information from interviews (directly during follow-up visits or by telephone) with patients, next of kin, witnesses, and attending physicians or from hospital/general practitioner records. Long-term vascular recurrence was defined as any event of fatal/non-fatal IS, transient ischaemic attack (TIA), fatal/non-fatal myocardial infarction, or other arterial thrombotic event. Recurrent IS was defined using the same criteria applied for the definition of the index event. myocardial infarction was diagnosed when at least two criteria among 1) ischaemic chest pain, 2) characteristic ECG changes, and 3) cardiac enzyme abnor-

malities were present. Diagnosis of TIA was made when the patient had reliably observed transient (<24 h) neurologic deficit of abrupt onset, without evidence of an underlying nonvascular cause, according to the consulting neurologist or the attending physician who evaluated the event by clinical and imaging methods. Deaths were classified using death certificates, medical records, and family interviews. In those cases in which it was difficult to make a precise determination of the cause of death, consensus was reached based on the best available information. If more than one recurrent event occurred, the first was used for calculation of the disease-free survival time. Primary endpoint was a composite of IS, TIA, myocardial infarction or other arterial events. Secondary endpoints were 1) brain ischaemia (IS or TIA) as well as 2) myocardial infarction or other arterial events (11).

Statistical analyses

Continuous data are presented as mean ± SD and categorical variables as frequencies. We compared means by the two-samples independent t-test. Pearson's χ^2 or Fisher's exact test were used for categorical variables. Categorical (multinomial) logistic-regression analysis was performed with FH status (FH of premature stroke, FH of premature myocardial infarction, and no FH of arterial thrombosis) as the dependent variable. The following covariates were entered into the analysis: age, sex, hypertension, hypercholesterolaemia, diabetes mellitus, current smoking habit, personal history of migraine and its subtypes (migraine without aura [MO] and migraine with aura [MA]), index stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, and thrombophilic status (*Model 1*). In a further multivariate logistic-regression analysis, the status of carrier of the G1691A mutation in the factor V gene (factor V Leiden), the G20210A mutation of the prothrombin gene, and circulating anti-phospholipid antibodies (aPL) were considered as separate covariates instead of a single all-or-none variable (*Model 2*). Finally, hazard ratios (HRs) were assessed by Cox proportional hazard models in multivariable analyses to detect the independent predictors of recurrence in the three subgroups defined by FH status using the same covariates reported above. Survival time was calculated from the date of the index event until the date of the outcome event of interest at follow-up or the last known date without the outcome event of interest. Analyses were performed with the statistic software packages SPSS (version 16.0 for Windows; SPSS Inc, Chicago, IL, USA). Two-sided values of $p < 0.05$ were considered significant.

Results

A cohort of 1,906 patients with first-ever IS was included in the IPSYS registry. Data on premature FH were missing in 25 patients. Baseline comparisons, thus, included 1,881 patients (mean age, 36.7 ± 7.1; men, 51.5%) of whom 85 (4.5%) had a FH of arterial thrombosis at young age. Of these, 33 (1.8%) had a FH of premature stroke (mean age, 37.0 ± 6.9; men, 39.4%), 45 (2.4%) a FH of premature myocardial infarction (mean age, 37.1 ± 8.0; men, 46.7%), and 7 (0.3%) a FH of both arterial events.

First-ever ischaemic stroke

Compared to patients with no FH of arterial thrombosis, those with FH of premature stroke were more often smokers, and more frequently carriers of the A1691 mutation of factor V gene and of the A20210 mutation of prothrombin gene, while females were more often oral contraceptives users.

Patients with FH of premature myocardial infarction had similar characteristics except they were more frequently carriers of circulating aPLs. When compared to patients with FH of premature myocardial infarction, those with FH of premature stroke less often had hypercholesterolaemia and circulating aPLs, but were more frequently carriers of the two prothrombotic genotypes (►Table 1).

As summarised by the FH status-covariate odds ratios (ORs) reported in ►Table 2, smoking habit was associated with a ~2-fold increased risk of FH of arterial thrombosis at young age (OR, 1.94; 95% confidence interval [CI], 1.21–3.09), an effect that was even more evident when the analysis was restricted to patients with FH of premature stroke (OR, 2.48; 95% CI, 1.21–5.11). In contrast, smoking habit did not associate with FH of premature myocardial infarction compared to the reference group of patients with no FH of thrombosis (*Model 1*). Similarly, although an underlying prothrombotic state turned out to increase more than three-fold the risk of FH of premature arterial thrombosis (OR, 3.66; 95% CI, 2.21–6.06), the magnitude of this effect was higher for the subgroup with FH of premature stroke (OR, 5.78; 95% CI, 2.79–11.97) than for the subgroup with FH of premature myocardial infarction (OR, 2.51; 95% CI, 1.26–5.02; *Model 1*). In particular, there was a clear differential effect of each prothrombotic abnormality on FH of premature stroke and on FH of premature myocardial infarction: while the former was influenced by prothrombotic genotypes (OR, 3.64; 95% CI, 1.31–10.10, for factor V Leiden mutation; OR, 8.40; 95% CI 3.35–21.05, for the A20210 mutation in the prothrombin gene), the latter was predicted by the presence of circulating aPLs (OR, 3.48; 95% CI, 1.61–7.51; *Model 2*).

Long-term recurrent thrombotic events

We followed 1,842 of the 1,881 patients (97.9%) included in the study group for a mean of 46.6 ± 38.6 months. Of these, 163 experienced recurrent events (primary endpoint) of which 86 had an IS, 8 a myocardial infarction, 67 a TIA, and two other arterial thrombotic events. We did not detect any difference in the distribution of recurrences in the subgroup of patients with no FH of early-onset thrombosis (n = 153, 8.7%) compared to the subgroup of patients with such a FH (n = 10, 12.3%; OR, 1.48; 95% CI, 0.74–2.92; p = 0.234), as well as to the subgroup of patients with FH of premature myocardial infarction (3, 6.8%; OR, 0.76; 95% CI, 0.23–2.51; p = 1.000). In contrast, recurrent events occurred

more frequently in the subgroup of patients with FH of premature stroke (6, 19.4%; OR, 1.02; 95% CI, 0.99–1.05; p = 0.051).

Among patients with primary outcome events, mean time interval between the index stroke and any arterial recurrence was shorter in the subgroup of patients with FH of premature arterial thrombosis (18.6 ± 11.9 months) and in the subgroup with FH of premature stroke (15.1 ± 12.2 months) than in the subgroup of patients with no FH of early-onset thrombosis (27.3 ± 27.9 months). Delay to the recurrent brain ischaemia (secondary outcome) was also shorter for the subgroup of patients with FH of premature arterial thrombosis (19.3 ± 12.4 months). None of these differences, however, was statistically significant (p >0.05; ▶Figure 1). The low number of myocardial infarction and other arterial recurrent events did not allow for separate analysis.

Finally, in the multivariate Cox proportion analysis, the status of carrier of any thrombophilic abnormalities tended to be a pre-

Table 1: Demographic and clinical characteristics of the study group. FH, family history; MO, migraine without aura; MA, migraine with aura; FV, factor V Leiden; PT, prothrombin. *, in women; seven patients with both FH of premature stroke and FH of myocardial infarction were excluded from the group of patients with FH of premature stroke and from that of patients with FH of myocardial infarction.

Variable	All (n = 1,881)	No FH of premature stroke or myocardial infarction (n = 1,796)	FH of premature stroke (n = 33)	P-value	FH of premature myocardial infarction (n = 45)	P-value
Hypertension	432 (23.0)	407 (22.7)	10 (30.3)	0.298	13 (28.9)	0.325
Diabetes mellitus	71 (3.8)	68 (3.8)	1 (3.0)	1.000	2 (4.4)	0.688
Current smokers	723 (38.4)	676 (37.6)	20 (60.6)	0.007	23 (51.1)	0.066
Hypercholesterolemia	469 (24.9)	445 (24.8)	5 (15.2)	0.306	16 (35.6)	0.099
History of migraine						
no migraine	1361 (72.4)	1294 (74.5)	24 (72.7)	0.817	36 (80.0)	0.489
MO	317 (16.9)	304 (17.5)	6 (18.2)	0.821	7 (15.6)	0.844
MA	144 (7.7)	139 (8.0)	3 (9.1)	0.744	2 (4.4)	0.576
Oral contraceptives*	346 (37.8)	321 (37.0)	12 (60.0)	0.036	12 (50.0)	0.195
Post-stroke therapy						
Anti-thrombotic medications				0.841		0.461
Anti-platelets	1433 (76.5)	1371 (76.7)	24 (72.7)		31 (68.9)	
Oral anti-coagulants	401 (21.4)	380 (21.3)	8 (24.2)		13 (28.9)	
Anti-hypertensive	432 (23.0)	407 (22.7)	10 (30.3)	0.298	13 (28.9)	0.325
Statins	329 (17.5)	307 (17.1)	4 (12.1)	0.640	14 (31.1)	0.014
Thrombolysis	127 (6.7)	121 (7.2)	6 (18.2)	0.031	0 (0.0)	0.070
Cause of stroke				0.527		0.463
Large-vessel disease	156 (8.3)	148 (8.2)	4 (12.1)		4 (8.9)	
Non-atherosclerotic vasculopathy	244 (13.0)	232 (12.9)	5 (15.2)		7 (15.6)	
Small-vessel disease	173 (9.2)	170 (9.5)	1 (3.0)		2 (4.4)	
Cardiac/transcardiac embolism	586 (31.2)	566 (31.5)	8 (24.2)		11 (24.4)	
Other diseases	722 (31.4)	680 (37.9)	15 (45.5)		21 (46.7)	
FV $_{G1691A}$				0.002		0.242
GG	1783 (95.9)	1709 (96.3)	27 (81.8)		42 (93.3)	
AG	77 (4.1)	66 (3.7)	6 (18.2)		3 (6.7)	
AA	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	
PT $_{G20210A}$				<0.001		0.878
GG	1792 (96.4)	1717 (96.8)	25 (75.8)		43 (95.6)	
AG	66 (3.6)	56 (3.2)	8 (24.2)		2 (4.4)	
AA	1 (0.1)	1 (0.1)	0 (0.0)		0 (0.0)	
Anti-phospholipids antibodies	123 (6.5)	112 (6.2)	2 (6.1)	1.000	9 (20.0)	0.002

dictor of recurrence (primary endpoint) in patients with FH of early-onset arterial thrombosis (HR, 4.47; 95% CI, 0.79–25.14; p = 0.089), as well as in patients with FH of premature stroke (HR, 4.33; 95% CI, 0.78–23.93; p = 0.092). Separate multivariate analyses for specific prothrombotic abnormalities were not conducted because of their low prevalence.

Discussion

Understanding the mechanisms causing familial clustering of ischaemic disease is a crucial step to target effective preventive interventions in family members. In this regard, current research leaves several important issues unclear. FH has often been considered as a covariate or a potential confounder in most epidemiologic studies, but not usually in direct association with disease endpoints. Even the most recent analyses based on data from the Framingham Study (14) and the Oxford Vascular Study (OXVASC)(15) have not considered FH of arterial thrombosis in this way. Our findings from the IPSYS, a hospital-based study with near-complete ascertainment and comprehensive FH assessment, provides, therefore, essential new information on the determinants of familial clustering of thrombotic disease.

What we have shown is that a familial aggregation of premature stroke or myocardial infarction is more likely for those probands who are current smokers and carriers of prothrombotic abnormalities. Intuitively, it appears probable, in spite of the inconsistent data of literature, that shared lifestyle risk factors, such as smoking, represent pathways through which FH may influence the risk of both cerebral and myocardial thrombosis. As to hypercoagulable states, patients suffering from these abnormalities are more prone to form an occlusive thrombus with clinical effects than those without such a predisposition, and the formation of a thrombus in itself is involved in the pathogenesis of both IS and myocardial infarction. What was rather unexpected is the observation that the influence of smoking and prothrombotic abnormalities on familial risk is not similar for all manifestations of arterial thrombosis. Actually, a notable finding from our data is that the distribution of such risk factors differs according to the subtype of vascular disease in the relatives, FV Leiden and PT A20210 variant predicting FH of premature stroke (with a possible prothrombotic influence of oral contraceptives), while circulating aPLs being the only coagulation abnormality associated with FH of premature myocardial infarction. Although the exact site-specific mechanisms of thrombosis are largely unknown, there is evidence supporting the hypothesis that the coagulative pathways favoring myocardial infarction differ from those predisposing to IS (16, 17). The same differential association was found for current smoking, which was a predictor of FH of premature stroke but not of FH of premature myocardial infarction. The biological explanation for this is far from obvious. It is possible that the individual perception of familial risk is higher for myocardial infarction than for stroke, which does not automatically lead to changed behavior in case of a FH of premature stroke, or, on the contrary, that some people with FH of premature stroke adopt a fatalistic outlook and make no efforts at all to decrease their risk.

Another novel finding of our study is that a history of early-onset thrombotic events in first-degree relatives, particularly when they involve the cerebral vasculature, is associated with increased propensity and shorter time-interval to recurrent thrombotic

Table 2: Conditional effect (ORs) of selected variables in the prediction of family history status. FH, family history. Covariates were age, gender, risk factors (hypertension, hypercholesterolaemia, diabetes mellitus, smoking), personal history of migraine and its subtypes [migraine without aura (MO) and migraine with aura (MA)], index stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, and thrombophilic status (*Model 1*); age, gender, risk factors (hypertension, hypercholesterolaemia, diabetes mellitus, smoking), personal history of migraine and its subtypes [MO and MA], index stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, and the status of carrier of the G1691A mutation in the FV (factor V Leiden) gene, the G20210A mutation of the prothrombin (PT) gene, and circulating anti-phospholipid antibodies (*Model 2*). Only significant values are reported. FH, family history.

	FH of premature thrombosis				FH of premature stroke				FH of premature myocardial infarction			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Smoke	1.94 (1.21 – 3.09)	0.005	1.92 (1.20 – 3.07)	0.006	2.48 (1.21 – 5.11)	0.013	2.48 (1.20 – 5.15)	0.014				
Prothrombotic state	3.66 (2.21 – 6.06)	<0.001			5.78 (2.79 – 11.97)	<0.001			2.51 (1.26 – 5.02)	0.009		
FV G1691A			2.64 (1.20 – 5.79)	0.015			3.64 (1.31 – 10.10)	0.013				
PT G20210A			4.00 (1.88 – 8.52)	0.001			8.40 (3.35 – 21.05)	<0.001				
Anti-phospholipids antibodies			2.36 (1.19 – 4.66)	0.014							3.48 (1.61 – 7.51)	<0.001

events in the proband, and that such recurrences may dependent on a pre-existent, likely familial, procoagulant state. Though of borderline significance, mainly because of the low incidence of recurrent events in our cohort, these findings are in line with what observed in previous studies on premature cardiovascular disease (18, 19), and implicate that intense prevention strategies might be especially justified in those individuals with a familial aggregation of ischaemic disease at young age. Searching for thrombophilic disorders appears also warranted in these cases (20, 21). Clearly, findings from our longitudinal analysis would need further confir-

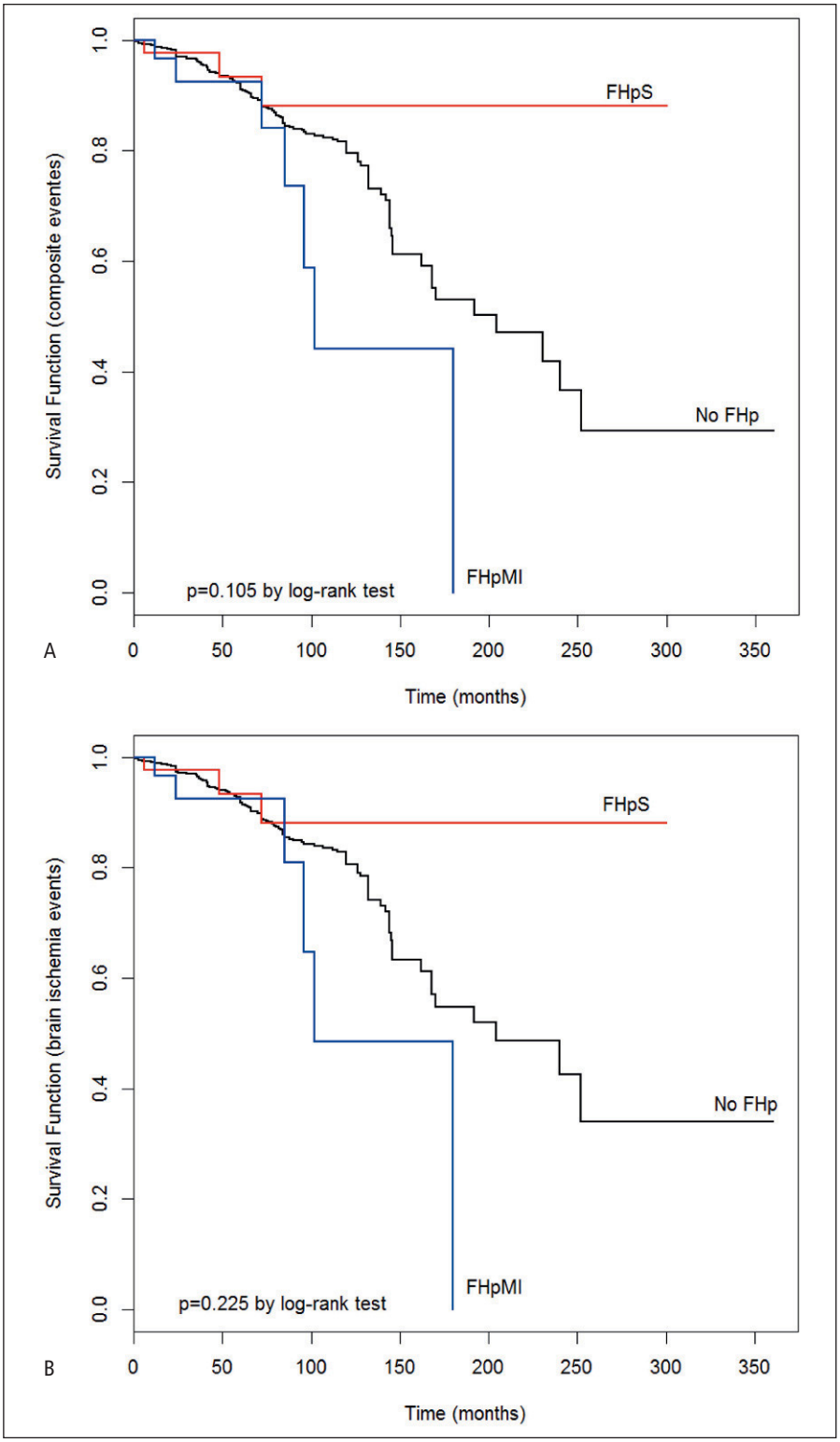

Figure 1: Time to recurrent events during follow-up. Kaplan-Meier estimates of recurrent thrombotic events (A) and of recurrent brain ischaemia (B) in young stroke patients with no family history of premature arterial thrombosis (noFHp), family history of premature stroke (FHpS) and family history of premature myocardial infarction (FHpMI).

mation, possibly by testing independent cohorts of patients with early-onset disease or by meta-analyses pooling individual subjects databases. However, since the IPSYS cohort is the largest series of patients with juvenile stroke currently available (22, 23), and the criteria we adopted for patients' selection and evaluation differ from those of other registries, we're aware that all these analyses could be inefficient.

The recruitment of a large cohort of consecutive patients in a multicentre setting is the main strength of our study. This approach gives a case series resembling the general population of young ischaemic strokes in Italy and minimises the potential selection bias due to enrollment from tertiary referral centers. Nevertheless, the absolute number of patients with FH of early-onset arterial thrombosis and their outcome events is relatively low, and this should be taken into account when interpreting our estimates. Furthermore, since we defined family history according to participant's and relatives' recall and not to formal medical record reviews, we cannot exclude the possibility that errors in recall may have influenced our results and limit their reproducibility. Although this shortcoming is noteworthy, participant's and relatives' recall more closely mimics the method used to obtain family history in clinical settings and may, therefore, be the most appropriate method to adopt for clinically useful studies. In this regard, despite consistent evidence supports family history as a risk factor for cerebrovascular disease, few standards address how this information should be collected, interpreted, and applied to clinical practice. Some details of the family history of stroke were also unavailable in our registry, particularly classification as ischaemic or haemorrhagic. However, thrombophilic disorders are unlikely to be associated to haemorrhagic stroke, making a spurious finding due to the inclusion of haemorrhagic strokes among family members unlikely. Another limitation is that we did not differentiate among families with events on the basis of the number of events and age of the events. Larger families are more likely to have a first degree relative with a positive history, introducing false associations with any risk factor associated with larger family sizes. Finally, although we assessed the risk factors suggested by previous studies, it remains possible that the observed associations may be attributable to familial aggregation of unidentified environmental, behavioural, lifestyle, and genetic factors, which differentially contribute to familial and sporadic IS. All these potential shortcomings are noteworthy. However, there are arguments to consider our results valid and biologically plausible.

In conclusion, patients with familial clustering of premature arterial thrombosis exhibit a distinct risk-factor profile, which differs according to the specific type of vascular event in the family members and has an impact on long-term prognosis. These observations have scientific implications for understanding the pathophysiology of familial aggregation of stroke and myocardial infarction. Although familial transmission of early-onset arterial thrombosis is likely to reflect different disease entities and pathogenic mechanisms that remain to be elucidated, we propose an underlying procoagulant state as major determinant. Basic research aimed at investigating the mechanisms by which FH of premature thrombosis might cause an ischaemic event should, therefore, focus on the haemostatic system and, perhaps, identify different pathways for different sites of arterial thrombosis. Further epidemiologic research could provide more insight in the different mechanisms of IS and myocardial infarction, taking into account the specificity of stroke subtypes and the potential interactions of the coagulative disorders with other predisposing conditions. Whether this might have clinical implications for the use of more targeted therapies aimed at reversing the prothrombotic phenotype in family members remains to be determined.

What is known about this topic?

- A family history (FH) of arterial thrombosis is associated with increased risk of ischaemic stroke (IS), particularly at young age.
- What factors predict FH of arterial thrombosis in patients with IS has not been extensively investigated.

What does this paper add?

- Familial aggregation of premature arterial thrombosis in young stroke patients is likely influenced by smoking habit and an underlying procoagulant state.
- In these subjects, factors influencing familial clustering of IS differ from those related to familial aggregation of myocardial infarction.
- Time-interval between the index event and thrombotic recurrence is shorter in stroke patients with FH of arterial thrombosis, particularly when they are carriers of procoagulant abnormalities.

Author contributions

Dr. Alessandro Pezzini had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Alessandro Pezzini, Mario Grassi. Acquisition of data: All authors. Analysis and interpretation of data: Alessandro Pezzini, Mario Grassi. Drafting of the manuscript: Alessandro Pezzini. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Alessandro Pezzini, Mario Grassi, Daniele Pepe. Obtained funding: Alessandro Pezzini, Corrado Lodigiani. Administrative, technical, or material support: Alessandro Pezzini. Study supervision: Alessandro Pezzini, Alessandro Padovani.

Conflicts of interest

None declared.

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