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Regular Article

Should women suffering from migraine with aura be screened for biological thrombophilia?: Results from a cross-sectional French study

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ABSTRACT

Introduction: Migraine, particularly migraine with aura (MA), is associated with a higher risk for ischemic stroke (IS). A procoagulant state may predispose to IS. Whether inherited biological thrombophilia are associated with migraine risk remains controversial.
Objective: To assess the risk of migraine without or with aura related to inherited biological thrombophilia adjusted for the main potential confounders.
Material and Methods: A cross-sectional study was conducted in 1456 French women aged 18 to 56 years, referred for biological coagulation check-up because of personal or familial venous thrombosis history. Between April 2007 and December 2008, all women answered a self-administered questionnaire to determine whether they had headache.
Results: There were 294 (20%) migrainous sufferers (including 71 [5%] with MA), 975 (67%) non migrainous women and 187 (13%) non migrainous headache women. Inherited thrombophilia were detected in 576 (40%) women, including 389 (40%) non migrainous women, 90 (40%) migraine without aura (MWA), 33 (46%) MA women and 64 (34%) non migrainous headache women. Factor V Leiden (FVL) i.e. F5rs6025 or Factor II G20210A (FIIL) i.e. F2rs1799963 mutation was detected in 296 (30%) non migrainous women and in 100 (34%) migrainous women of which 27 had MA. There was a significant association between MA and FVL or FIIL mutations (adjusted OR = 1.76 [95% CI 1.02-3.06] p = 0.04) whereas this association in MWA and in non migrainous headache women was not significant. There was no significant association between migraine and other biological thrombophilia.
Conclusion: FVL or FIIL mutations were more likely among patients suffering from MA. Whether biological thrombophilia screening should be systematically performed in women suffering from MA remains to be determined.

Introduction

Ischemic stroke (IS) is one of the leading causes of death, disability and health expenditures worldwide [1]. Identifying the main risk factors for IS and understanding the underlying patho-physiological mechanisms is a major concern in terms of both preventive and therapeutic strategies with important public health issues.

Migraine, particularly migraine with aura (MA), is associated with a higher risk of IS in young women [2–4]. The nature of the association between these diseases remains poorly understood. Possible mechanisms predisposing migraine patients to IS may be vascular, neuronal or related to coagulation abnormalities [5].

Presence of a procoagulant state due to a platelet hyperaggregability or to a higher prevalence of inherited coagulation abnormalities (i.e. Factor V Leiden (F5rs6025), Factor II G20210A (F2rs1799963) mutations, protein C, protein S, antithrombin deficiencies) is one of the various proposed hypotheses [6].

Previous studies have investigated the prevalence of activated biological thrombophilia in patients with migraine but results remain controversial. Although some authors [7,8] failed to show a strong association between inherited biological thrombophilia and migraine, other observations showed a high prevalence of genetic thrombophilia, particularly FVL mutation, in migrainous patients [9,10].

In this context, the present study was conducted in order to investigate the association of migraine with inherited thrombophilia in women who had biological thrombophilia screening for personal venous thromboembolic disease or severe familial history of venous thrombosis.

Abbreviations: APC, Activated Protein C; FVL, Factor V Leiden (F5rs6025); FIIL, Factor II G20210A (F2rs1799963); IHS, International Headache Society; IS, Ischemic stroke; MA, Migraine with aura; MWA, Migraine without aura; VTE, venous thromboembolism.

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Material and Methods

Study Population

A cross-sectional study was performed in the hemostasis outpatient unit. All women aged 18 to 56 years, who were referred for biological coagulation check-up to the hemostasis unit in our hospital between April 2007 and December 2008, were consecutively included (n = 1456). Women were invited to answer a self-administered questionnaire, if they were no pregnant, no post-menopausal, not referred for acute or chronically bleeding, personal history of ischemic stroke, myocardial infarction or cerebral venous thrombosis.

The questionnaire was divided into three parts:

- The first part included questions regarding weight, height, smoking, personal and family medical history including migraine and stroke.
- The second part included headache questions in order to determine whether the subject had headache, the age at first symptoms, the frequency of headache, the treatments used in case of attack, and to diagnose migraine. This part of the questionnaire has been previously validated and has been used in the Head-HUNT Study [11] (available in annex). Patients who answered "yes" to the question "Have you had headache during the last 12 months?" were classified as headache sufferers. Then, based on the answers to precise clinical questions about the headache episodes, they were classified into two groups as either migraine- or non-migrainous- headache. The two diagnoses were mutually exclusive. In the groups of migrainous women, women were diagnosed as suffering from MA according to the definition of the Head-Hunt study. Indeed, the pain phase of migraine with aura is often shorter that in migraine without aura. Therefore we accepted a diagnosis of migraine with aura in subjects who reported 'often visual disturbance prior to headache' if they otherwise fulfilled the criteria for migraine without aura, even if they had attacks that lasted less than 4 h.
- The third part contained information regarding gynecological history including, the use of previous and current hormonal contraceptives, the age at first contraception and the number of pregnancy.

Questionnaire responses were filled in by women and checked by physicians in consultation.

Among a total of 1456 women who completed the questionnaire and the biological thrombophilia screening, the statistical analysis consisted of 975 (67%) non migrainous women, 294 (20%) migraine sufferers including 71 with MA (5%) and 187 (13%) non migrainous headache women. Final analyses were therefore performed in the four following groups: 1) non migrainous women; 2) migrainous women without aura; 3) women with MA and 4) non migrainous headache women (Fig. 1).

Thrombophilia Screening

Blood was drawn into vacuum tubes containing 129 mmol/L sodium citrate as anticoagulant except for cell blood counts which were performed on EDTA blood samples (all vials were BD Vacutainer ®). Laboratory evaluation included blood cell count, prothrombin time (Neoplastine CI ®, Diagnostica Stago), activated partial thromboplastin time with lupus anticoagulant detection (APTT BioMérieux ®, PTTLA Diagnostica Stago ®), fibrinogen chronometric activity, Prothrombin activity, Antithrombin heparin cofactor activity (COAMATIC AT400 ®, Biogenic), protein C chromogenic activity (Berichrom Protein C ®, Dade Behring), protein S functional activity (STA-Staclot Protein S ®, Diagnostica Stago) and free protein S antigen (STA-Liatest Free Protein S ®, Diagnostica Stago) plasma levels. All these tests were measured on a STAR ® analyzer (Diagnostica Stago). Activated Protein C (APC) resistance in the presence of factor V deficient plasma was analyzed with a functional assay (Coatest APC ® Resistance V, Instrumentation Laboratory, USA) on a STAR ® analyzer. APC resistance was defined as an APC ratio below 2.0, after evaluation of the distribution of the APC ratio in a large population of normal individuals in our laboratory (data not shown). FVL and FII20210A gene mutations were identified using genomic DNA extracted from 5 ml citrated blood by standard procedures. Patients with abnormal APC ratio had been tested for FVL gene mutation. The mutation analysis was performed on a LightCycler ® instrument (Roche) using LightCycler ® Primer/Hybridization Probes and LightCycler-DNA Master Hybridization Probes (Roche Molecular biochemicals, Germany) according to the manufacturer's recommendations. Immunoglobulin IgG and IgM anticardiolipin antibodies and homocysteinemia were also measured. Diagnosis of thrombophilia was confirmed on a second blood sampling.

Informed consent for the biological check-up was provided by all study participants.

Statistical Analyses

Quantitative variables, including women's age and age at first migraine, were given as means (standard deviation) and qualitative variables including body-mass index, family history of migraine, family

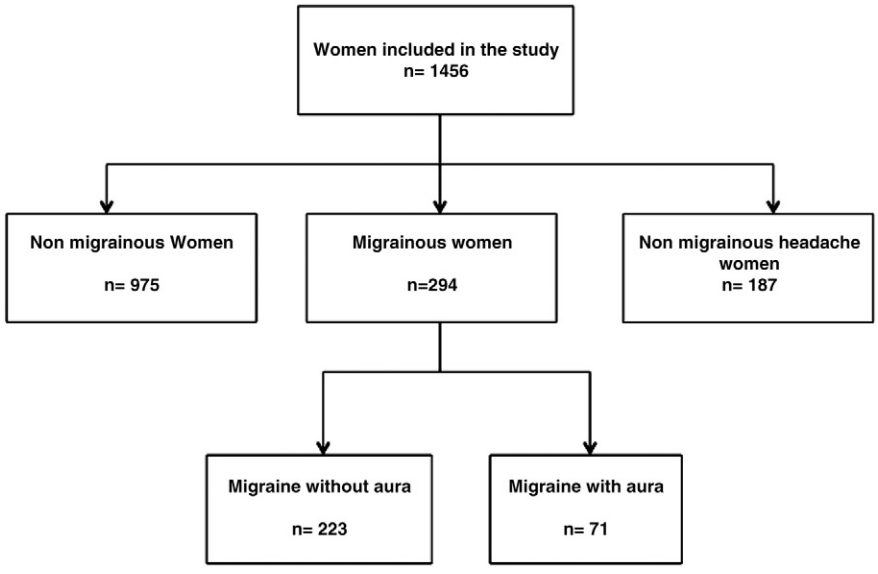

Fig. 1. Diagram of the flow of participants within the study.