Family history of hypertension is not an independent genetic factor predisposing to ischemic stroke subtypes

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Received 15 June 2006; received in revised form 9 September 2006; accepted 14 September 2006

Abstract

Objectives: The effect of family history of hypertension (FHx HT), as a genetic factor predisposing to some ischemic stroke subtypes and independently of hypertension as risk factor, has never been studied.

Methods: A positive FHxHT was searched in 472 patients (312 men, 160 women; mean [S.D.] age, 67.9 [11.4] years) consecutively admitted for a first-ever ischemic stroke (348) or transient ischemic attack (TIA) (124) due to small vessel disease (SVD, 180), large vessel disease (156), or cardioembolism (136). In this population and in three age bands, the genetically transmitted vascular risk factors, age, gender and the ischemic stroke subtypes were compared between those with and without a positive FHxHT.

Results: None of the risk factors was associated with a positive FHxHT, except for hypertension in the whole population (68.9% vs. 48.7%; \( p = 0.001 \)) and in the <65 year-old patients (72.5% vs. 39.5%; \( p < 0.001 \)). Regarding the stroke subtypes, a positive FHxHT was only associated with SVD in the subgroup of <65 year-old patients (odd ratios (OR), 2.07; 95% confidence interval (CI), 1.01 to 4.25; \( p = 0.045 \)). However, this finding disappeared in a logistic regression analysis, which only retained hypertension as independently associated with SVD.

Conclusions: FHxHT is not an independent genetic factor predisposing to some aetiological stroke subtypes.

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Keywords: Stroke; Family history; Stroke subtypes; Genetics; Hypertension

1. Introduction

Genetic studies on ischemic stroke should be focused on the different pathogenic subtypes, and for each of them, they should determine which genetic factors may act either by predisposing to conventional risk factors, or by modulating the effects of such risk factors on the end organs, or by a direct independent effect on stroke risk [1,2]. Hypertension, the most potent risk factor for clinical and silent stroke, can be genetically determined [3]. A higher prevalence of hypertension and stroke found in parents of hypertensive probands suggests that these two conditions might share common genetic factors [4]. In contrast to coronary artery disease, ischemic stroke is a heterogeneous disease due to different causes, mainly large vessel atherosclerotic disease, small vessel disease (SVD) and cardioembolism. A possible association between these aetiological ischemic stroke subtypes and a family history of hypertension (FHxHT) has never been studied and this might provide more pathophysiological information about the heritability of stroke.

The aim of this study is to determine whether the presence of FHxHT is associated with a specific aetiological ischemic stroke subtypes, and if so whether this association is independent of hypertension as risk factor, thereby suggesting a specific gene mutation for stroke other than that responsible for the family transmissibility of hypertension. Given that the stroke phenotype may be expressed differently according to the age of stroke onset, we performed the same analysis in patients younger than 65 years, patients of intermediate age (between 65 and 75 years) and older patients (≥75 years).
2. Methods

This study was performed in a university hospital in which the vast majority of stroke patients are admitted in the department of neurology. We evaluated 875 consecutive patients with a first-ever ischemic stroke or transient ischemic attack (TIA) defined by the National Institute of Neurological Disorders and Stroke [5]. Aetiology of the qualifying ischemic event was defined according to the TOAST criteria as large vessel disease (LVD), small vessel disease, cardioembolic stroke (CES), other (any cause other than LVD, SVD, or CES), or undetermined (unknown or uncertain aetiology) [6]. Patients with undetermined or other determined aetiology were excluded from the study. In addition to age and gender, the following vascular risk factors likely to be genetically determined were evaluated: hypertension (current treatment with antihypertensive drugs or two blood pressure values $\geq 140/90 \text{mmHg}$ at least 5 days after the stroke onset), hyperlipidemia (total cholesterol $\geq 6.50 \text{mmol/L}$ or triglycerides $\geq 2.03 \text{mmol/L}$) and diabetes mellitus (fasting glucose level $\geq 6.0 \text{mmol/L}$ or current treatment).

A family history of hypertension in the first-degree relatives was obtained using a structured interview by the treating neurologist at the time of stroke. The subjects were asked whether their first-degree relatives were alive or dead, whether they were or had been hypertensive, and whether they were taking or had taken antihypertensive drugs. The first-degree relatives were interviewed whenever possible, and especially when the patients were unable to document their family history because of aphasia or decreased consciousness. In case the first-degree relatives had died or were no longer in contact with the patient, the data were obtained from their close relatives. For ethical reasons, it was not possible to access the relatives’ medical chart that show previous records of blood pressure check-ups or any antihypertensive therapy taken by them.

2.1. Data and statistical analysis

In the whole population, we compared the mean age of patients with and without FHxHT. We calculated the odd ratios (OR) for a positive FHxHT in three categories of age at the time of stroke onset (<65 years, 65–74 years, $\geq$ 75 years) and in each of the three main ischemic stroke subtypes (LVD, SVD, CES) affecting the proband in the whole population of patients and in the three pre-defined categories of age. We studied the presence of a positive FHxHT in relation to gender, diabetes, hypertension and hyperlipidemia in the whole population of patients and in the three categories of age. Categorical and numerical variables were compared by chi-square or Wilcoxon rank sum test. A logistic regression was performed to determine which risk factor, statistically significant in the univariate analyses, was independently associated with the SVD stroke subtype. This analysis was carried out with a continuous variable (age) and categorical variables (hypertension and FHxHT) as independent variables and SVD stroke subtype as the dependent variable. All statistical tests were two-tailed and performed by SPSS software (SPSS Inc., Chicago, IL). A $p$ value less than 0.05 was considered as statistically significant.

3. Results

In this population of 875 patients, 403 were excluded because ischemic stroke was due to undetermined (322) or other determined (81) aetiology. Therefore, 472 patients (312 men, 160 women; 348 stroke, 124 TIA; mean [S.D.] age, 67.9 [11.4] years; median age, 68.8 years, range, 30–93 years) were included, who had one of the three main aetiological subtypes defined by the TOAST classification: LVD in 156 patients (17.8%), SVD in 180 (20.6%) and CES in 136 (15.5%). There was no significant difference between the included and excluded patients for age (mean [S.D.] age, 67.9 [11.4] vs. 67.5 [12.7]) and gender (men, 312 [66.1%] vs. 244 [60.5%]). A positive FHxHT was present in 90 (19.1%) of the 472 selected patients. Race was Caucasian in all patients.

Patients with a positive FHxHT were significantly younger than those without (mean [S.D.] age, 64.9 [10.2] vs. 69.2 [11.8] years, $p=0.002$). A positive FHxHT was significantly associated with age less than 75 years at the time of stroke onset (OR, 0.42; 95% confidence interval [CI], 0.23–0.75; $p=0.003$). There were no significant differences between the patients with and without a positive FHxHT for gender, diabetes and hyperlipidemia. In patients with a positive FHxHT, more patients were hypertensive (68.9%) than normotensive (31.1%). Hypertension was significantly associated with a positive FHxHT in the whole population (68.9% vs. 48.7%; $p=0.001$) and in the <65 year-old patients (72.5% vs. 39.5%; $p<0.001$). A positive FHxHT was not associated with LVD or CES in the whole population of patients or within the three age bands. For small vessel disease, a significant association was found in the <65 year-old patients (OR, 2.07; 95% CI, 1.01–4.25; $p=0.045$) but not in the whole population. We performed a logistic regression to determine which variable was independently associated with SVD. When age as continuous variable, hypertension as risk factor and FHxHT were considered, only hypertension was independently associated with SVD ($\beta$-coefficient, $-1.102$; $p=0.001$).

4. Discussion

This study was hospital-based and the exclusion of less severe stroke patients who are not referred to hospital may have biased our results. However, the consistent results observed in population- and hospital-based studies suggest that inclusion bias is not a major problem for the genetic study of stroke [7]. Our study was not controlled because, like others [7], we have purposely performed case–case comparisons of patients to avoid the recall bias of case-control studies,
stroke patients being more aware of any family history than controls. We have also categorized the patients according to three age bands of stroke onset. These cut-offs are arbitrary, and others have chosen similar [8–10] or different limits [7,11,12]. Another limitation of this type of study is the difficult ascertainment of family history due to the lack of access to the relatives’ charts to provide reliable data.

Our data show that ischemic stroke or TIA occurred at a younger age in the patients with a positive FHxHT. If ischemic stroke is genetically determined by the presence of such family history, the earlier expression of cerebrovascular phenotype in young patients might be the explanation.

Subjects with a positive FHxHT are more likely to be hypertensive [13] and genetic factors account for one-third to one-half of the risk of hypertension [14,15], which is a potent risk factor for SVD. Therefore, hypertension might be considered as a “synthetic trait” under genetic control [16] contributing to the risk of SVD. Deletion polymorphism of the angiotensin-converting enzyme gene has been reported in patients with a history of stroke [17] and those with lacunar stroke [18]. The effect of FHxHT, as a genetic factor predisposing to some ischemic stroke subtypes and independently of hypertension as risk factor, had never been studied so far [19]. Such effect would suggest a specific gene deletion leading to ischemic stroke irrespective of the presence of traditional risk factors and more particularly hypertension for lacunar stroke. Our study shows that FHxHT is associated with hypertension as a risk factor and SVD as aetiology for the index cerebral ischemia in the subgroup of patients younger than 65 years of age. However, the logistic regression only identified hypertension and not FHxHT as independent factor for SVD. Therefore, this clinical study does not seem to support the hypothesis that FHxHT is an independent risk factor per se with a gene mutation, other than that conducting to heritable hypertension, for a specific ischemic stroke subtype and especially small vessel disease.

Acknowledgement

We thank Mrs. Valérie Cornil for her invaluable help to collect the clinical data.

References