Gene Mutations and Stroke in the Young Adult

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Background: The purpose of this study is to evaluate the existence of the genetic mutation in the different types of cerebral and spinal strokes in previously healthy young adults. *Methods:* We performed a retrospective study of the medical records of 35 young adults who presented to our institution with the diagnosis of acute cerebrovascular insult. We defined the localization of their stroke, specified their risk factors, defined their genetic mutation, and correlated these variables to assess their significance in the predisposition of stroke in the young. *Results:* We found that the MTHFR and Factor V gene mutations are the most likely mutations to be associated with cerebral strokes in young adults. Spinal strokes are also associated with beta fibrinogen, factor XIII, and prothrombin II mutations. We did not find that a homozygous gene mutation is more thrombogenic than its heterozygous component. *Conclusions:* We concluded that the major etiologies for stroke in young adults were multiple gene mutations rather than systemic illnesses. We found out that mutation of the MTHFR gene in isolation or in combination with other gene mutations is the most important risk factor for stroke in the young. **Key Words:** Young—stroke—hypercoagulable state—MTHFR—Factor V.

Introduction

Stroke in young adults is not a rare disease. Multiple studies associate cerebral stroke with gene mutations.[1-11] The cerebrovascular pathology seems to be directly related to the gene mutation rather than systemic illnesses or contributory risk factors. The genetic mutations associated with strokes are multiple and work in combination rather than as isolated genes. Studies tend to associate some genes with certain types of strokes being arterial, venous, single or multiple, cerebral, or spinal. It is important to recognize the presence of genetic mutations in strokes in young adults to initiate early aggressive anticoagulation, to counsel patients on the risk of strokes, to advise on additional contributory risks, to relate the prognosis, and to screen predisposed relatives of patients.

Material and Methods

We reviewed retrospectively the medical files of 35 patients who presented with the clinical picture of cerebral or spinal stroke to our institution over the last 2 years. Patients' age ranged between 16 and 50 years. Seventy percent were more than 30 years of age. Sixty percent were males and 40% were females. Less than10 % of the patients had mild hypertension, dyslipidemia, or new onset diabetes mellitus. These diseases occurred in the same group of patients, and they were recently diagnosed and adequately controlled. None of the patients had systemic conditions that predisposed them to stroke such as polycythemia rubra vera, connective tissue disorder, malignancy, antiphospholipid syndrome, valvular heart disease, atrial fibrillation, or carotid stenosis. One patient was suspected to have Sjogren syndrome, and 1 patient was on oral contraceptive drugs for a limited period. All the patients underwent a transthoracic echocardiography, and none of them had a patent foramen ovale.

All patients underwent magnetic resonance imaging (MRI) and magnetic resonance angiography of cerebral

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and carotid arteries. Magnetic resonance venography of the brain or MRI of the spine was performed in patients where the clinical presentation required these studies. The blood studies requested included routine hematology, chemistry, and serology studies. Antinuclear antibody (ANA), perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA), cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA), anticardiolipin antibodies, erythrocyte sedimentation rate (ESR), homocysteine level, and the panel of hypercoagulable studies were done. The complete battery of genetic analysis, that is, Methylenetetrahydrofolate reductase (MTHFR) (C677T), MTHFR (A1298C), Factor V Leiden (G1691A), Factor V (H1299R), Factor II (G20210A), Factor XIII, V34L, alpha fibrinogen 455G>A, beta fibrinogen, PAI-1: 4G/5G (plasminogen activator inhibitor), HPA1 a/b (platelet receptor), ACE I/D (angiotensin converting enzyme), were all analyzed. We compared the different genetic abnormalities to the different clinical presentations, pathologic findings in the blood studies, and the radiographic studies performed. Statistical analysis was performed to correlate the genetic mutations, single or in combination, with the other abnormal studies and with the location of the stroke (Table 1).

Statistical Analysis

Chi-square tests were used in the analyses to compare the distribution of gene mutations between the 4 types of lesions (cerebral arterial, cerebral venous, spinal, and small vessel disease) and within the whole sample. The proportion of MTHFR gene mutations (MTHFR A1298C and MTHFR C677T) and Factor V gene mutations to the total number of gene mutations were compared across the 4 lesion types. A 4-sample test for equality of proportions was calculated on the different stroke types. Fisher test for count data was used because of the small values in some of the cells (<5).

Results

Clinical, laboratory, and radiographic data from 35 patients younger than 50 years of age who presented with acute cerebral or spinal stroke were analyzed. All patients had normal routine hematology and chemistry studies, negative ANA, p-ANCA, c-ANCA, anticardiolipin antibodies, ESR, and c-reative protein. One patient had positive lupus anticoagulation factor, and another patient had slightly elevated homocysteine level. Electrocardiogram and echocardiogram were normal in all patients except septal hypertrophy in 1 hypertensive patient and congenital hypertrophic cardiomyopathy in another patient.

Fifty-two percent of the patients had anterior circulation cerebral arterial strokes, of which 60% were single large strokes and 40% multiple hemispheric strokes. Twenty-six percent had cerebral venous sinus thrombosis, 11% had posterior circulation arterial strokes, and 11% had spinal artery occlusion.

Most patients expressed multiple gene mutations, only a minority had an isolated mutation. Ninety-four percent of patients had an MTHFR mutation, of which 47% had MTHFR A1298C mutation and 53% had MTHFR C677T mutation, only 3 patients (9%) had both mutations simultaneously. The MTHFR gene mutation is the most common pathology in all the patients with strokes occurring in all cases of spinal strokes, in 81% of patients with cerebral arterial strokes, and in 77% of patients with venous strokes. The difference in MTHFR mutation between the lesion types was, however, not statistically significant ($P = .54$).

Forty-nine percent of the patients had the Factor V mutation, of which 63% had the Factor V Leiden G1691A mutation and 37% had the Factor V H2199R mutation. The proportion of Factor V mutations occurred in 50% of patients with arterial infarcts, 45% in patients with venous cerebral infarcts, and 50% in patients with spinal infarcts. The difference is, however, not statistically significant ($P = .39$).

Thirty-two percent had the ACE mutation, 34% the PAI-1 mutation, 23% the Factor XIII mutation, 17% the alpha fibrinogen mutation, 8.6% the prothrombin G20210A mutation, and 7.5% the beta fibrinogen mutation. All except 1 patient had either the MTHFR or the Factor V mutation abnormality.

The beta fibrinogen mutations were found only in patients with spinal cord and not cerebral strokes. Alpha fibrinogen abnormalities were restricted to cerebral arterial strokes and occurred in 27% of patients. Patients with venous strokes did not express either the alpha or the beta fibrinogen mutations.

Factor XIII gene mutations predominated in spinal strokes (75%), and was found only in 18% of patients with arterial cerebral strokes and was absent in patients with venous thrombosis. The PAI-1 gene mutation was present in 50% of patients with arterial strokes, 22% in patients with venous strokes, and only in 1 patient with spinal stroke.

Prothrombin II gene mutation is rare, occurring in only 1 patient with spinal infarction, 3 patients with cerebral arterial infarcts, but lacking in patients with venous infarcts. The ACE mutation predominated in cerebral arterial infarcts (36% of patients), and was rarely expressed in venous thrombosis or spinal infract.

An analysis was carried out to investigate whether all gene mutations contribute equally to development of stroke. A chi-square test comparing all gene mutations revealed a significant difference in the number of mutations present in the sample ($P = .001$), with the higher contributor being the MTHFR, which represents 30% of the total mutations.

There is no significant difference in the number of patients with at least 1 homozygous gene (n = 19) and the number of patients with only heterozygous genes (n = 16; $P = .61$). The occurrence of a homogenous mutation in any gene was 55%, whereas 45% were heterogonous, suggesting that both homogenous and