Ischemic Stroke Subtypes and Thrombophilia in Young and Elderly Brazilian Stroke Patients Admitted to a Rehabilitation Hospital

Francisco Javier Carod-Artal, MD, PhD; Simone Vilela Nunes, MD; Dalton Portugal, MD; Tania Virginia Fernandes Silva, MD; Antonio Pedro Vargas, MD

Background and Purpose—We sought to examine ischemic stroke subtypes and prevalence of thrombophilia in Brazilian stroke patients.

Method—A total of 130 consecutive young and 200 elderly stroke patients were studied.

Results—Prevalence of thrombophilia was, respectively: protein S deficiency (11.5% versus 5.5%), protein C deficiency (0.76% versus 1%), resistance to activated protein C (2.3% versus 3.5%), mutation in V Leiden factor (1.5% versus 2%), antithrombin III deficiency (0% versus 0%), lupus anticoagulant (0% versus 0.5%), anticardiolipin antibodies (3% versus 10%; P=0.01), hyperhomocysteinemia (31.5% versus 53.5%; P=0.0001), mutation of the MTHFR gene in homozygosis (10% versus 5%), and heterozygosis (27.6% versus 41.9%; P=0.01).

Conclusion—Prothrombotic conditions were more frequent in stroke of undetermined cause. (Stroke. 2005;36:2012-2014.)

Key Words: epidemiology • stroke • thrombophilia • thrombosis

Stroke subtypes in South America seem to be different from other regions of the world.1 Stroke in young adults (15 to 45 years of age) is a rare condition.2,3 Hypercoagulable states may account for a small proportion of ischemic strokes,4 particularly in younger individuals with stroke of undetermined cause. Ethnic differences in markers of thrombophilia have been described in Western countries.5 The influence of thrombophilia in ischemic stroke has been poorly studied in South America.

The aim of this study was to evaluate the prevalence of vascular risk factors and ischemic stroke subtypes in young and elderly stroke patients and analyze the prevalence of thrombophilia in patients with ischemic stroke in a stroke reference Brazilian hospital.

Materials and Methods

From January 2002 to January 2004, 130 consecutive ischemic stroke patients (mean age 33.8 years; range 15 to 45 years of age) were admitted to the Neurology Department at Sarah Hospital in Brasilia Federal District. Patients were referred by local neurologists and health centers from Federal District, with an estimated catchment area of 2.5 million inhabitants. A prospective analysis design was developed. Clinical data were compared with a group of 200 ischemic stroke patients from a prospective Stroke Registry (mean age 61.5 years of age) consecutively admitted to the hospital during 2003.

Data were collected on vascular risk factors and diagnostic stroke subtypes. All patients underwent a diagnostic protocol for ischemic stroke, including ECG, chest x-ray films, carotid echo-Doppler (100%), transthoracic (100%) or transesophagial echocardiogram (64% of young versus 31% of elderly), computed tomography scan, and thrombophilia studies. Brain MRI was performed when necessary in 94 young (magnetic resonance angiography in 46.6%) and 44 elderly patients. Thrombophilia studies included fasting plasma levels of protein C, protein S, antithrombin III, levels of homocysteine, resistance to activated protein C (APC), IgG anticardiolipin (ACL) antibodies, and lupus anticoagulant (LA). Genetic tests for the V Leiden factor and C677T methylene tetrahydrofolate reductase gene mutations (MTHFR) were obtained in all subjects. Additional biochemical studies included serology for syphilis (Venerereal Disease Research Laboratory), Chagas disease, and antinuclear antibodies in all patients.

Screening of thrombophilia was done at 3 months after the acute stroke event to exclude an acute-phase response. Repeated testing during the convalescent state was performed when an abnormal result was observed. The diagnosis of any anticoagulant deficiency was based on established in-house laboratory reference ranges for protein C (70% to 130%), protein S (65% to 130%), antithrombin III (80% to 120%), LA (33% to 42%), ACL antibodies (positive IgG >10 IgG phospholipid units/mL; positive IgM >10 IgM phospholipid units/mL). Homocysteinemia was diagnosed when the mean of its serum level was >13 μmol/L.

Trial of Org 10172 in Acute Treatment (TOAST) criteria were used to define stroke subtype. We included patients with positive markers of thrombophilia without other known causes of stroke in the group of stroke of undetermined cause. Risk factor comparison for young and elderly subjects was performed using t tests for continuous variables and χ² test and Fisher exact test for categorical variables. A 2-tailed P value of <0.05 was considered statistically significant.
Results

During 2002 to 2003, 833 stroke patients were admitted to our hospital (56.3% men; mean age 56.77 years; SD 16.6). A total of 180 (21.6%) were 45 years of age; 72.2% of young stroke patients (130) had an ischemic infarction and were included in this study. Demographic and vascular risk factors of the study population are shown in Table 1; thrombophilia studies appear in Table 2. Protein S deficiency was the most prevalent thrombophilic condition in young patients. Prothrombotic conditions were more prevalent in stroke of undetermined cause ($P<0.001$).

We analyzed the overall thrombophilia states (any combination of protein C, protein S, or antithrombin III deficiencies, resistance to APC, positive LA, or a mutation in the factor V of Leiden). Twenty-one young (16.1%) and 26 elderly (13%) patients had potential thrombophilic states (odds ratio [OR], 0.78; CI, 0.4 to 1.51; $P=0.423$). When this subgroup was analyzed, 15 young (16.7%) and 6 elderly stroke patients (9.4%) with stroke of undetermined origin had a thrombophilia (OR, 0.7; CI, 0.24 to 1.97; $P=0.456$).

Discussion

This study examines the association between all major causes of thrombophilia and pathogenic subtypes of acute ischemic stroke in stroke patients. Published data on prevalence of thrombophilic states in stroke vary widely in Western countries, ranging from 0% to 24%.6

Our study revealed a high prevalence of cryptogenic stroke in young stroke patients and no association between inherited thrombophilias and any of the pathogenic subtypes of ischemic stroke in old stroke patients. Only protein S deficiency was associated with stroke of undetermined cause in young patients. Prothrombotic conditions were more prevalent in stroke of undetermined cause ($P<0.001$).

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should focus on the possible role of acquired thrombophilias (LA, ACL antibodies) in the pathogenesis of specific etiological subtypes of ischemic stroke (embolism from or via the heart, small vessel disease) in the young.

The strength of our study is that we prospectively evaluated a cohort of 330 ischemic stroke patients. However, the potential occurrence of a selection bias can never be entirely ruled out because this epidemiological study was done in a stroke reference hospital. Several thrombophilic states were more common among the elderly: ACL antibodies and hyperhomocysteinemia. Levels of homocysteine and ACL antibodies may increase with age. In conclusion, although distributions of stroke subtype and of conventional risk factors were different between young and elderly subjects, thrombophilic states did not clearly differ and could not explain those differences.

### References


### TABLE 2. Thrombophilia Studies in the Stroke Population

<table>
<thead>
<tr>
<th></th>
<th>Young n=130</th>
<th>Elderly n=200</th>
<th>(P, \chi^2)</th>
</tr>
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<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
<td></td>
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<tr>
<td>Protein S deficiency</td>
<td>15 11.5</td>
<td>11 5.5</td>
<td>0.001</td>
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<tr>
<td>Chagas serology</td>
<td>14 10.8</td>
<td>51 25.5</td>
<td>0.001</td>
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<td>Sickle cell trait</td>
<td>6 4.6</td>
<td>4 2</td>
<td></td>
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<tr>
<td>Anticardiolipin antibodies</td>
<td>4 3.1</td>
<td>20 10</td>
<td>0.018</td>
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<tr>
<td>APC resistance</td>
<td>3 2.3</td>
<td>7 3.5</td>
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<td>Factor V Leiden mutation</td>
<td>2 1.5</td>
<td>4 2</td>
<td></td>
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<td>VDRL</td>
<td>2 1.5</td>
<td>8 4</td>
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<tr>
<td>Antinuclear antibodies</td>
<td>2 1.5</td>
<td>12 6</td>
<td></td>
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<tr>
<td>Protein C deficiency</td>
<td>1 0.8</td>
<td>2 1</td>
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<tr>
<td>LA</td>
<td>0 0</td>
<td>1 0.5</td>
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<tr>
<td>Antithrombin III deficiency</td>
<td>0 0</td>
<td>1 0.5</td>
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<tr>
<td>Hyperhomocysteinemia</td>
<td>41 31.5</td>
<td>107 53.5</td>
<td>0.0001</td>
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<tr>
<td>Mutation gene MTHFR</td>
<td>49 37.7</td>
<td>93 47</td>
<td></td>
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<tr>
<td>Homocigosis</td>
<td>13 10</td>
<td>10 5.05</td>
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<tr>
<td>Heterocigosis</td>
<td>36 27.7</td>
<td>83 41.9</td>
<td></td>
</tr>
<tr>
<td>Mean homocysteine level, SD</td>
<td>15.03 (SD 14.87)</td>
<td>16.66 (SD 9.56)</td>
<td></td>
</tr>
</tbody>
</table>

VDRL indicates Venereal Disease Research Laboratory.
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