A Prospective Study of Cerebral Ischemia in the Young

Analysis of Pathogenic Determinants

Antonio Carolei, MD; Carmine Marini, MD; Edoardo Ferranti, MD; Marco Frontoni, MD; Massimiliano Prencipe, MD; Cesare Fieschi, MD; and the National Research Council Study Group

Background and Purpose: The etiology of stroke in the young is different from that in older patients and remains unknown in almost one third of the cases. To gain further insight into both pathogenic and etiologic determinants, we prospectively studied a large number of consecutive young adults with focal cerebral ischemia.

Methods: Three hundred thirty-three patients aged 15–44 years with transient ischemic attack or ischemic stroke within the 8 weeks before hospital admission were recruited and investigated by using a standardized protocol of clinical evaluation, blood tests, electrocardiography, echocardiography, chest roentgenography, and brain computed tomography. Presumed etiology was diagnosed by prospectively applied criteria.

Results: Women predominated (61%) among patients under 35 years of age, mainly due to the frequency of cerebral ischemia related to oral contraceptive use, while men outnumbered women (60%) among patients over that age because of a higher prevalence of atherothrombotic disease. Potential cerebral embolism of cardiac origin was the presumed cause of stroke in 23.7%, but conventional sources of embolus were found only in 7.5% of cases. There was a low prevalence of atrial fibrillation among young patients with cerebral ischemia. Mitral valve prolapse was found in 8.4%, as expected, predominantly (71.4%) among the younger patients. The prevalence of stroke over transient ischemic attack was proportional to the likelihood of cardiac embolism. Acute alcohol intoxication was considered a precipitating factor in only three patients. The percentages of cerebral ischemia attributed to arterial dissection (0.3%), oral contraceptive use in women (8.1%), migraine (1.2%), and other associated medical diseases (1.5%) were lower than reported in recent clinical series.

Conclusions: Two different groups of pathogenic determinants predominate in younger women and in older men, supporting public health measures aimed at strict medical control of the recognized cerebrovascular risk factors. (Stroke 1993;24:362–367)

Key Words • cerebral ischemia • risk factors • young adults

It is well known that cerebral ischemia may occur in young adults1 and that the spectrum of etiologies in young adults is different from that in older patients.2–10 The cause remains unknown in almost one third of the cases, despite extensive diagnostic investigations.3,4,6,7,9,10 However, our knowledge of cerebral ischemia in young patients is based on literature data, which have several drawbacks. Among these is the relatively few patients included in each study, in none being more than 150.3,4,6,7,9–11 In addition, there are important differences among studies, including the age limits for admission. Furthermore, a selection bias may be present because some studies performed in large tertiary-level referral centers have considered consecutive cases, while others have not. In many previous studies, evaluation was not prospective and standardized.

To gain further insights into the pathogenic and etiologic determinants of ischemic stroke, we prospectively studied a large consecutive hospital-based series of young adults with focal cerebral ischemia. We evaluated the presence and characteristics of cerebrovascular risk factors and associated medical diseases by means of a standardized protocol including, besides medical history, results of cardiac and neurodiagnostic tests, and we applied prospective criteria to establish the diagnosis.

Subjects and Methods

Three hundred thirty-three young adults between 15 and 44 years of age who had their first transient ischemic attack (TIA) or stroke within the 8 weeks preceding admission into the hospital were prospectively recruited and investigated between April 1984 and March 1988. Seven neurological departments (at Milan, Pavia, Padua, Genoa, Florence, Rome, and...
L’Aquila) participated in the study, contributing all patients admitted.

TIA was defined as a focal neurological deficit resolving completely within 24 hours.12 Stroke was defined as a focal neurological deficit of sudden onset that persisted beyond 24 hours in surviving patients.12 Care was taken to exclude as TIA, for the purpose of this study, transient global amnesia, loss of consciousness, drop attacks, and focal symptoms associated with migraine headache.13

The standardized protocol included medical history, results of both cardiac and neurological evaluations, laboratory blood tests (red and white blood cell counts; hematocrit; platelet count; erythrocyte sedimentation rate; concentrations of blood glucose, serum creatinine, urea nitrogen, electrolytes, total cholesterol, high density lipoprotein cholesterol, and triglycerides; and serological tests for syphilis), electrocardiography (ECG), M-mode and/or two-dimensional (2D) echocardiography, chest roentgenography, and computed tomography (CT) of the brain. Levels of protein C, protein S, and antithrombin III were not routinely assessed. Cerebral angiography was highly recommended in patients without a recognized source of cardiac embolism and appropriate hypodensity on a brain CT scan.

Cerebrovascular risk factors such as arterial hypertension, diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, cigarette smoking, alcohol abuse, illicit drug use, migraine with and without aura, and oral contraceptive use were screened, together with cardiac abnormalities and associated medical diseases.

Risk factors and criteria for diagnosing cardiac abnormalities are defined in Appendix A.14–18 Cardiac abnormalities were also reviewed and categorized by the same cardiologist, according to their embolic potential,19–22 as conventionally recognized as embolic, possibly embolic, and probably nonembolic.

All patients’ records were independently reviewed by two of us. To assess the more likely etiology of cerebral ischemia, patients were considered as belonging to one of the following six groups:

1. Atherothrombotic. Angiography of the symptomatic cerebral arterial territory showed stenosis of ≥50%, occlusion, or an ulcerated plaque of the internal carotid artery or intracranial occlusion without evidence of cardiac abnormalities.6,9,10 An atherothrombotic etiology was also presumed if the patient had two or more atherogenic risk factors,6,9,10,11 without arteriographic lesions, in the absence of other identifiable causes.

2. Cardioembolic. A potentially likely or possible cardiac source of emboli was present without evidence of extracranial or intracranial arterial stenosis and with or without concomitant ipsilateral intracranial occlusion on angiography.

3. Mixed. Extracranial or intracranial atherothrombotic stenosis or occlusion was evident on angiography, and conventional or possible embolic cardiac abnormalities were present.

4. Other. Angiographic evidence of arteritis, fibromuscular dysplasia, and arterial dissection was present with hematologic, infectious, or autoimmune diseases and with oral contraceptive use or migraine with aura at the time of the event. The deficit was not fully reversible within 24 hours and was associated with a corresponding hypodensity on a brain CT scan, in the absence of other identifiable causes.

5. Undetermined. There was evidence of only one atherogenic risk factor and associated medical disease or probably nonembolic cardiac abnormalities alone.

6. Unknown or idiopathic. There was no evidence of atherogenic risk factors and associated medical diseases, in the absence of atherothrombotic, cardioembolic, and other abnormalities predisposing to cerebral ischemia.

Statistical evaluations were performed by means of cross-tabulation, Pearson’s $\chi^2$ test, and the Wilcoxon rank test when appropriate.

**Results**

There were 173 men and 160 women (male:female ratio, 1:1). Mean age was 35.7±7.4 years. Men were more numerous ($n=122$) than women ($n=80$) among those aged over 35 years, whereas women ($n=80$) outnumbered men ($n=51$) among those under that age. One hundred forty-one patients (42.3%) had TIA, and 192 (57.7%) presented with stroke. Seven patients (2.1%) died within 30 days. Brain CT revealed a hypodensity, likely ischemic, in the appropriate hemisphere in 148 (44.6%) of the 332 patients who underwent this diagnostic procedure. Cerebral angiography was performed in 240 patients (72.1%) and showed abnormalities in 95 (39.6%).

Risk factors were distributed as reported in Table 1. Cigarette smoking, hypertriglyceridemia, and alcohol abuse ($p<0.0001$) were more frequently associated with male sex and migraine history ($p<0.0001$) with female sex. Arterial hypertension ($p<0.0001$), hypercholesterolemia ($p<0.002$), and hypertriglyceridemia ($p<0.001$) prevailed in the older patients. Oral contraceptive use, in women, was more frequent ($p<0.001$) among those under 35 years of age. Acute alcohol intoxication occurred in three male patients and was associated with left atrial enlargement in one case.

Associated medical diseases were found in 24 patients (7.2%) (Table 2) and were considered etiologically determinant in five.

ECG was performed in all patients but one, while M-mode and 2D echocardiography were carried out in 323 patients. ECG was abnormal in 64 cases, whereas echocardiography showed abnormalities in 83. Consequently, one or more cardiac abnormalities were diagnosed in 101 patients (30.3%).

A conventional cardiac source of cerebral emboli was found in 25 patients (7.5%) and possibly embolic cardiac abnormalities were detected in 54 (16.2%), whereas a probably nonembolic source was found in 22 patients (6.6%) (Table 3). Five patients had both atrial fibrillation and a prosthetic heart valve ($n=4$) or mitral stenosis ($n=1$). A left ventricular thrombus was detected in three stroke patients: one had an acute myocardial infarction, one nonischemic dilated cardiomyopathy, and one chronic ischemic heart disease. Mitral valve prolapse (MVP) was diagnosed in 28 patients, 20 of whom were younger than 35 years. Myxomatous changes were found in one TIA and four stroke patients. MVP was associated with Marfan’s syndrome in one case and with fibromuscular dysplasia in another.

Of the 101 patients with cardiac abnormalities (Table 3), the majority ($n=73$) had a stroke as the first-ever
episode on admission \( p<0.001 \). The percentage of strokes was higher \( p<0.0001 \), Wilcoxon rank test) in the subgroups of patients with either a conventional (84%) or possible (72.2%) cardiac source of emboli than in those with probably nonembolic (59.1%) or no (51.3%) cardiac abnormalities. Strokes prevailed \( n=18 \) over TIA \( n=10 \) also in patients with MVP.

According to our criteria (Table 4) an atherothrombotic etiology was found in 110 patients (33.1%); the diagnosis was based on angiography in 50 patients and on the presence of two or more atherogenic risk factors in 60. A cardioembolic etiology was confirmed in 64 patients (19.2%). Fifteen patients (4.5%) had a mixed atherothrombotic and cardioembolic etiology. Cerebral ischemia was attributed to other causes in 27 patients (8.1%); migraine with aura was the presumed cause in four patients, isolated hematologic and autoimmune diseases were determinant in five, oral contraceptive use was the likely cause in 13 female patients, arteritis in two, fibromuscular dysplasia alone in two, and arterial dissection in one.

A definite etiology for cerebral ischemia was therefore reached in 216 cases (64.9%). The diagnosis was undetermined in 66 patients (19.8%). In 51 patients (15.3%) presenting with negative medical history, laboratory tests, cardiac evaluation, and cerebral angiography the etiology remained unknown.

Again, cardioembolic \( p<0.02 \) and mixed \( p<0.01 \) etiologies (Table 5) were more frequent in the stroke subgroup, whereas unknown causes were more commonly found \( p<0.015 \) among TIA patients (Table 5). Thirty-day mortality was observed in stroke patients only.

**Discussion**

As in previous studies,10,23 in our series women predominated (61%) among patients under 35 years of age, mainly because of the presence of nonatherogenic risk factors such as oral contraceptive use and migraine. Nonetheless, the prevalence of oral contraceptive use among our female patients (12.5%) was lower than previously reported.3,5-7,9,10,23

Men outnumbered women (60%) among patients aged over 35 years.4,5 In these patients early atherothrombotic disease appeared to predominate, thus making this older subgroup more similar to the general population.7,19,20

Cardiac abnormalities were detected in 30.3% of our patients with routine ECG and echocardiography.11,24,25 Potential cerebral embolism of cardiac origin was diagnosed in 23.7% of our patients. With reference to the conventional sources alone, the percentage became notably lower (7.5%). In the same subgroup the relative frequency of ventricular thrombi, detected by echocardiography, was as anticipated (12%).19,20

### TABLE 1. Prevalence, Percentages, and Sex Distribution of Risk Factors in 333 Patients With Cerebral Ischemia According to Age

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No.</th>
<th>%</th>
<th>Male/female (n/n)</th>
<th>Sex distribution (male/female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking (&gt;20/day)</td>
<td>117</td>
<td>35.1</td>
<td>82/35*</td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia (&gt;150 mg/dl)</td>
<td>113</td>
<td>33.9</td>
<td>76/37*</td>
<td></td>
</tr>
<tr>
<td>Cardiac abnormalities</td>
<td>101</td>
<td>30.3</td>
<td>53/48</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia (&gt;250 mg/dl)</td>
<td>66</td>
<td>19.8</td>
<td>40/26</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>63</td>
<td>18.9</td>
<td>39/24</td>
<td></td>
</tr>
<tr>
<td>Migraine history</td>
<td>50</td>
<td>15.0</td>
<td>9/41*</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>20</td>
<td>12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse (&gt;100 g/day)</td>
<td>41</td>
<td>12.3</td>
<td>39/2*</td>
<td>10/2 (29.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9</td>
<td>2.7</td>
<td>8/1</td>
<td></td>
</tr>
</tbody>
</table>

\( p<0.001 \) different from global male/female ratio (173/160).

\( \text{f} p<0.001, \text{g} p<0.002, \text{h} p<0.0001 \) different prevalence between age subgroups.

### TABLE 2. Associated Medical Diseases in 24 Patients With Cerebral Ischemia

<table>
<thead>
<tr>
<th>Code</th>
<th>Disease</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \beta )-Thalassemia</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse intravascular coagulation</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Ilicit drug use</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Ilicit drug use and latent syphilis</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Essential thrombocytopenia</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Glucose 6-phosphate dehydrogenase deficiency and latent syphilis</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Hemodialysis and chronic renal failure</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Hyperandrogenism</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Hypogammaglobulinemia</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>Kugelberg-Welander disease</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>Marfan’s syndrome</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>Microcystosis</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>Nephrotic syndrome</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>Peripartum anemia</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>Peripheral vascular disease</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>Renal transplant</td>
<td>1</td>
</tr>
<tr>
<td>17</td>
<td>Latent syphilis</td>
<td>2</td>
</tr>
<tr>
<td>18</td>
<td>Systemic lupus erythematosus</td>
<td>3</td>
</tr>
<tr>
<td>19</td>
<td>Werlhof’s disease</td>
<td>1</td>
</tr>
</tbody>
</table>
Arrhythmias were found in 2.7% of our patients, thus proving an extremely low prevalence of both nonvalvular and valvular atrial fibrillation in cerebral ischemia in young patients.\(^2\)

MVP was found in 8.4% of our patients, typical of the frequency reported in previous general population studies.\(^18\) This valvular abnormality prevailed (71.4%) in our younger patients, thus confirming the relevance of MVP in ischemia in persons under 35 years of age.\(^7\) As opposed to other reports,\(^19,20\) we found more strokes (64.3%) than TIs. Myxomatous valvular degeneration was rather infrequent (1.5%), as already reported,\(^11,20\) MVP was not a major cause of stroke in young adults in our hospital-based series.

The majority of patients with cardiac abnormalities had a first-ever stroke (72.3%) on admission.\(^19,20\) Stroke prevalence over TIA was proportional to the likelihood of cardiac embolism.

Acute alcohol intoxication was considered a precipitating factor\(^27\) in three patients, two with an atherothrombotic and one with a cardioembolic etiology.

The prevalence of carotid or vertebral arterial dissection, particularly relevant according to some reports,\(^5,7-10\) was negligible in our series, possibly because most of the patients with head and neck trauma were referred to neurosurgical departments.

Specifically looked for associated medical diseases were determined to be of etiologic importance in only a few cases (1.5%).\(^3\)

The percentages of cerebral ischemia attributed to either oral contraceptive use in female patients (8.1%) or migraine with aura (1.2%) were lower than previously reported.\(^3,4,9,10\)

Thirty-day mortality (2.1%) was lower than previously reported,\(^6,7,10,11\) probably because of the inclusion, in our series, of TIA patients.

The percentage of both undetermined and unknown causes for cerebral ischemia, lower in stroke (27.1%) than in TIA (46.1%) patients, although within the range found in other studies,\(^3-5,10\) might also depend on drawbacks of our diagnostic protocol.

Patients with normal echocardiography (74%) did not undergo repeat examination with contrast transeosophageal echocardiography to rule out a patent foramen ovale.\(^28-30\) Although this and other possible sources of paradoxical cerebral embolism could not be excluded, no clinical evidence of venous thrombosis in the legs was found in any of our cases before the event. We could also have missed left atrial appendage thrombi and atherosclerotic lesions in the ascending aorta and proximal aortic root, which can cause cerebral embolism.\(^30,31\)

We did not routinely screen our patients for antiphospholipid antibodies,\(^11\) and therefore we might have overlooked additional cases with systemic lupus erythematosus or lupuslike disease. More hematologic causes could have been diagnosed with extensive laboratory investigations.\(^8,11\)

Nevertheless, our study demonstrates that at least two different groups of pathogenic determinants predominate in younger women (15–34 years) and in older men (35–44 years), supporting public health measures to prevent cerebral ischemia.
TABLE 5. Distribution and Associated Medical Diseases According to Diagnostic Groups in 333 Patients With Cerebral Ischemia

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Distribution</th>
<th>Associated medical diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With angiographic evidence</td>
<td>110*</td>
<td>33.1</td>
</tr>
<tr>
<td>With two or more risk factors</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>64†</td>
<td>19.2</td>
</tr>
<tr>
<td>Mixed</td>
<td>15</td>
<td>4.5</td>
</tr>
<tr>
<td>Other</td>
<td>27</td>
<td>8.1</td>
</tr>
<tr>
<td>Arteritis</td>
<td>2</td>
<td>3, 13</td>
</tr>
<tr>
<td>Fibromuscular dysplasia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hematologic and autoimmune diseases</td>
<td>5</td>
<td>1, 9, 12, 14, 18</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>13‡</td>
<td>19.8</td>
</tr>
<tr>
<td>Undetermined</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Probable nonembolic cardiac abnormalities</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Asymmetrical septal hypertrophy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>51</td>
<td>15.3</td>
</tr>
</tbody>
</table>

Associated medical diseases coded as in Table 2.
*Includes 18 patients with probably nonembolic cardiac abnormalities.
†Includes one patient with fibromuscular dysplasia and mitral valve prolapse.
‡Includes one patient with history of migraine.

In young adults, strict medical control of the recognized cerebrovascular risk factors should be attempted: 1) performing a preventive cardiac evaluation, considering the high yield of noninvasive investigations,11,21,22,24,25 2) reducing blood pressure in hypertensive patients,3 3) suggesting dietary measures to lower serum total cholesterol and serum triglyceride levels, 4) recommending cessation of smoking, 5) if there must be oral contraceptive use, prescribing agents with the lowest doses of estrogens and withdrawal in the presence of potential cardiac sources of emboli, and 6) encouraging preventive screening and control of impaired glucose tolerance and diabetes mellitus.

Appendix A

Definitions of Risk Factors

Arterial hypertension. Diastolic blood pressure of ≥90 mm Hg, according to the Hypertension Detection and Follow-up Program,24 before or at recruitment, out of the acute phase.

Diabetes mellitus. Diagnosis documented by medical records before or at recruitment, according to the National Diabetes Data Group.15

Hypercholesterolemia. Based on a fasting blood cholesterol level of >200 mg/dl at recruitment.

Hypertriglyceridemia. Based on a fasting blood triglyceride level of >150 mg/dl at recruitment.

Cigarette smoking. Smoking habit during the last 2 months of >20 cigarettes/day.

Alcohol abuse. Alcohol intake during the last 2 months of >100 g/day or acute alcohol intoxication during the 24 hours preceding the onset of TIA or stroke.

Migraine. History of migraine with or without aura, as defined by the Headache Classification Committee,16 previously coded as classic or common migraine.17

Oral contraceptive use. Use of oral contraceptives during the last 6 months.

Isolated arrhythmias and impulse conduction disorders. Premature ectopic beats, atrial fibrillation, paroxysmal supraventricular tachycardia, Wolff-Parkinson-White syndrome, bundle branch block, or atrioventricular block diagnosed by electrocardiography, as interpreted by a cardiologist.

Valvulopathies. Mitral stenosis and/or insufficiency and aortic leaflet lesions diagnosed by echocardiography, as interpreted by a cardiologist.

Mitrail valve prolapse. Echocardiographic diagnosis by a cardiologist. Restrictive criteria18 were used, requiring valve prolapse to be evident at an M-mode examination or in at least two positions at 2D echocardiography. When evident on apical
four-chamber views, the leaflet junction had to stay in the left atrium, not in the mitral annulus plane. Myxomatous degeneration of the mitral valve was considered present when the 2D echocardiography short-axis view showed thickened valve leaflet(s) (≥5 mm) with excessive mobility and redundancy.

**Bacterial endocarditis.** Present when the patient had fever, at least two positive blood cultures, a new or changing heart murmur, and/or typical echocardiographic vegetations.

**Hypertensive heart disease.** Echocardiographic diagnosis by a cardiologist, according to the occurrence of left ventricular hypertrophy or asymmetrical septal hypertrophy or left atrial enlargement in patients under treatment for arterial hypertension.

**Chronic ischemic heart disease.** Angina pectoris or previous Q and non-Q myocardial infarction diagnosed by history.

### Appendix B

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