Etiology, Prognosis, and Hemostatic Function After Cerebral Infarction in Young Adults

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A. Johns, FNZIMLT, and J. Smith, BSc

We retrospectively evaluated 66 patients younger than 40 years of age who presented with acute nonhemorrhagic cerebral infarction (n=63) or transient ischemic attacks (n=3) to determine the possible etiology and long-term outcome at a mean follow-up interval of 3 years after initial presentation. A probable cause for the stroke was identified in 24 patients (36%); this group included one woman with a history of recurrent spontaneous abortions and a positive test for the presence of the lupus anticoagulant. We performed detailed hemostatic investigations at follow-up in 38 (90%) of the remaining 42 patients in whom the cause of the stroke was unknown or uncertain; results of the basic hemostatic screening tests (including that for fibrinogen) were uniformly normal. All 38 patients demonstrated a normal fibrinolytic response as measured by tissue plasminogen activator release to a standard venous occlusion stress test; concentration of the inhibitor of tissue plasminogen activator was not increased. No abnormalities in the concentrations of the inhibitory proteins C or S or antithrombin III were identified, and none of the 38 patients had evidence of a lupus anticoagulant. Neurologic recovery was complete or the residual disability mild in 46 of 59 (78%) patients. Overall prognosis was excellent and independent of whether a precipitating factor for the stroke could be identified. (Stroke 1989; 20:477-482)

Nonhemorrhagic cerebral infarction (NHCI) before the age of 40 years accounts for <4% of all strokes in our community.1 In contrast to older patients, atherosclerosis is an uncommon cause of NHCI in younger adults.2,3 Cerebral emboli from a cardiac source are generally regarded as the most important cause of NHCI in this age group.4 Many other disorders are less commonly associated with NHCI, but the etiology remains unexplained in a significant proportion of patients even after extensive investigations.5-10 There is uncertainty about which associated disorders (particularly migraine11,12 or mitral valve prolapse13,14) are to be considered responsible in individual cases of NHCI.

Hemostatic disturbances have been reported in young stroke patients. Platelet hyperaggregability has been demonstrated in both the acute phase and following an episode of cerebral ischemia.15-18 Non-vasculitic cerebral infarction has been associated with lupus anticoagulant (LA) activity or the presence of anticardiolipin antibodies19-24; defective fibrinolysis has been reported as a variable finding.25-27 There has also been interest in naturally occurring anticoagulant proteins associated with recurrent or familial venous thrombosis. Isolated case reports have identified reductions in the concentrations of proteins C or S as potential risk factors for NHCI,28,29 but the precise significance of reduced levels of these inhibitory proteins and antithrombin III remains to be defined.

The prognosis of young adults with NHCI is favorable.30 A 5.2% cumulative stroke plus death rate has been reported after 3 years.31 We retrospectively reviewed our experience of NHCI in young adults. Our objective was to compare prognoses in patients in whom the etiology of NHCI was established with those in whom the etiology was unknown. We have attempted to define the importance of hemostatic factors in those patients in whom no other precipitating abnormality could be identified.

Subjects and Methods

Between January 1980 and December 1987 80 patients younger than 40 years with stroke or transient ischemic attack (TIA) were referred to the Department of Neurology at Auckland Hospital; 14 patients had an intracerebral hemorrhage and are excluded from subsequent analysis. Stroke was
defined as the acute onset of a focal neurologic deficit with no explanation other than a vascular cause after inpatient investigation and follow-up, and we did not consider patients with a diagnosis of complicated migraine and without a fixed neurologic deficit after 24 hours. Sixty-three patients had symptoms lasting >24 hours, and three patients had one or more TIAs. All 66 patients were examined by a neurologist; 63 had computed tomography and 36 had cerebral angiography. All 66 patients had one or both of these investigations as well as cardiologic examination, electrocardiography, and chest x-ray. M-mode or two-dimensional echocardiography was performed in 49 patients. A diagnosis of mitral valve prolapse was made by echocardiographic criteria. Contrast echocardiography was not routinely performed. All 66 patients had routine hematology profile and investigations of erythrocyte sedimentation rate and serum glucose, urea, and creatinine concentrations, and most had protein electrophoresis, autoantibody screen, and syphilis serology.

Information from the patient clinical file (verified wherever possible at follow-up) was obtained on personal history of hypertension, cardiac disease, diabetes, or migraine or a family history of premature vascular disease. Drug intake, including use of oral contraceptives (OCs), recreational drugs, and smoking, was detailed. The relation of NHCI to an episode of migraine, alcohol consumption, neck trauma, pregnancy, or preceding viral infection was recorded.

Follow-up information was obtained in 59 patients at a mean of 36 (range 3–96) months; 51 were personally interviewed and examined, information was obtained by telephone from five patients or a relative, three patients had died, and seven were lost to follow-up. At the time of follow-up, disability was graded as complete recovery if absent, mild if it did not interfere with activities of daily living (ADL), moderate if disability interfered significantly with ADL, and severe if the patient depended on others for most ADLs.

Coagulation studies were undertaken at follow-up in those patients in whom the etiology of NHCI remained unknown or uncertain. Whole blood was collected into Vacutainer tubes (Becton Dickinson Labware, Lincoln Park, New Jersey) containing 105 mM buffered citrate. A portion of the sample for LA testing was double-spin at high speed before immediate testing or storage at −30°C for later batch analysis. The remainder of the sample, centrifuged at 2000g for 10 minutes at 4°C before separation into aliquots and storage at −30°C, was used for routine coagulation tests and the measurement of the concentration of selected coagulation inhibitors. Fibrinolytic parameters were measured using plasma samples collected before and after a 10-minute venous occlusion at midsystolic-diastolic blood pressure. A blood sample used for assaying functional tissue plasminogen activator (tPA) activity was acidified before storage.

<p>| Table 1. Clinical Features of 66 Young Adults With NCHI at Time of Referral to Auckland Hospital |</p>
<table>
<thead>
<tr>
<th>Feature</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>Single NHCI</td>
<td>51</td>
</tr>
<tr>
<td>TIA and NHCI</td>
<td>2</td>
</tr>
<tr>
<td>Multiple NHCI</td>
<td>10</td>
</tr>
<tr>
<td>Cardiac source of emboli</td>
<td>2</td>
</tr>
<tr>
<td>Treated malignant hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>1</td>
</tr>
<tr>
<td>No cause established</td>
<td>6</td>
</tr>
<tr>
<td>Single TIA</td>
<td>2</td>
</tr>
<tr>
<td>Multiple TIAs</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are number of patients. NHCI, nonhemorrhagic cerebral infarction; TIA, transient ischemic attack.

The routine coagulation tests included activated partial thromboplastin time (APTT) (Auto APTT reagent, General Diagnostics, Durham, New Jersey), prothrombin ratio (PR) (rabbit brain thromboplastin ISI 1.13), and thrombin-based fibrinogen assay. The Exner kaolin clotting time (KCT) was used to screen for LA activity. The presence of an anticardiolipin antibody was assessed as previously described. Chromogenic assays were used to determine concentrations of antithrombin III and protein C. Protein C concentration was also measured immunologically by Laurell rocket electrophoresis using a rabbit antibody raised in our laboratory. Total and free protein S antigen concentrations were measured by rocket electrophoresis using antisera obtained from American Diagnostica (Epping, Australia). Fibrinolytic capacity before and after venous occlusion was assessed using an enzyme-linked immunosorbent assay for tPA antigen and a chromogenic assay test kit for functional tPA activity and the corresponding inhibitor (KabiVitrum, Stockholm, Sweden). The normal ranges included all values within two standard deviations of the mean from an appropriately selected sample of normal individuals from the local population. The mean±SEM normal values for the fibrinolytic assays were determined from 19agematched controls.

A paired t test was used to compare the results from before and after venous occlusion; an unpaired t test was used to compare the fibrinolytic parameters of our patients with those of the age-matched controls.

Results

Our patients comprised 35 females and 31 males, mean age 27.3 (range 11–39) years; there was no significant difference in mean age between females and males. Table 1 summarizes the clinical features of the patients at the time of referral. The carotid circulation was involved approximately twice as frequently as the posterior circulation. Of the 36 patients examined by cerebral angiography, an occluded vessel or a partial filling defect was demonstrated in 20, of whom four had complete internal...
related to the NHCI). Two patients had had further TIAs; both patients had focal arterial abnormalities, related to trauma in one but of uncertain pathogenesis not typical of atherosclerosis, fibromuscular dysplasia, or arteritis in the other. Only one patient had experienced a second NHCI; although the cause of his illness remains uncertain, he has demonstrated a remarkable capacity for recovery after each NHCI, and closure of a patent foramen ovale (PFO) has not prevented further NHCIs. No further events had occurred in the other 53 patients. Forty-six of 59 patients (78%) had made a complete recovery or had only a mild disability, 10 had a moderate disability, and no long-term survivor depended on others for ADL (although the patient who died after 2 years had been severely disabled).

The degree of disability was no worse in the group of 24 patients in whom an etiology of NHCI had been established. Epileptic seizures occurred in five patients and were difficult to control in one. The five patients with a cardiac source of emboli received long-term anticoagulants or antplatelet agents. An additional 20 patients were treated for <1 year with either anticoagulants (n=11) or antplatelet agents (n=9).

Hemostatic tests were performed on 38 (90%) of the 42 patients in whom the cause of the neurologic episode was unexplained; 31 had had a normal APTT and PR and 14 were negative for LA activity at presentation, but none had had more detailed hemostatic investigations. The follow-up results for these 38 patients with unknown cause of NHCI are summarized in Tables 3 and 4. Results of the screening tests were normal and concentrations of the three coagulation inhibitors were not reduced in any of the 38 patients; the anticardiolipin antibody assay was negative and the KCT was normal in all patients. Before venous occlusion, concentrations of tPA antigen and tPA inhibitor and tPA functional activity did not differ significantly from normal. All 38 patients demonstrated an increase in tPA con-

### Table 2. Etiology of Nonhemorrhagic Cerebral Infarction or Transient Ischemic Attack in 24 Patients With Identified Cause or Likely Predisposing Factor

<table>
<thead>
<tr>
<th>Etiology</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol intoxication*</td>
<td>7</td>
</tr>
<tr>
<td>Heart disease previously unrecognized</td>
<td>5</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatic valvular disease</td>
<td>1</td>
</tr>
<tr>
<td>Nonrheumatic aortic incompetence</td>
<td>1</td>
</tr>
<tr>
<td>Atrial septal defect and atrial fibrillation</td>
<td>1</td>
</tr>
<tr>
<td>Neck trauma or manipulation†</td>
<td>4</td>
</tr>
<tr>
<td>Pregnancy or postpartum</td>
<td>2</td>
</tr>
<tr>
<td>Migraine at onset</td>
<td>2</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Lupus anticoagulant‡</td>
<td>1</td>
</tr>
<tr>
<td>Herpes zoster-related arteritis</td>
<td>1</td>
</tr>
<tr>
<td>Focal arterial abnormality§</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are number of patients.
*All males, ictus within 18 hours of consumption of >60 g alcohol.
†One patient also had previous neck irradiation.
‡Also oral contraceptive use and mild rheumatic valvular heart disease.
§Uncertain cause.

carotid occlusions (bilateral in one); the remaining angiograms were normal, without evidence of atherosclerosis. The median interval from ictus to angiography was 5 days in those with a positive result and 10 days in those with a normal result. A probable cause of NHCI or TIA was identified in 24 of the 66 patients (36%, Table 2). Possible factors contributing to NHCI of uncertain significance were identified in an additional 21 (32%; OC use in four, smoking in five, previous migraine in six, two of these factors in six). The remaining 21 patients (32%) had no identified contributing factors.

Follow-up information was available on 59 of the 66 patients (89%). Three had died (two deaths were related to the NHCI). Two patients had had further TIAs; both patients had focal arterial abnormalities, related to trauma in one but of uncertain pathogenesis not typical of atherosclerosis, fibromuscular dysplasia, or arteritis in the other. Only one patient had experienced an additional NHCI; although the cause of his illness remains uncertain, he has demonstrated a remarkable capacity for recovery after each NHCI, and closure of a patent foramen ovale (PFO) has not prevented further NHCIs. No further events had occurred in the other 53 patients. Forty-six of 59 patients (78%) had made a complete recovery or had only a mild disability, 10 had a moderate disability, and no long-term survivor depended on others for ADL (although the patient who died after 2 years had been severely disabled).

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### Table 3. Hemostatic Test Results at Follow-up in 38 Patients With Nonhemorrhagic Cerebral Infarction of Unknown Cause

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Range</th>
<th>Mean±SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>32±0.5</td>
<td>22-37</td>
<td>29.5±0.68</td>
</tr>
<tr>
<td>PR</td>
<td>1±0.08</td>
<td>0.8-1.2</td>
<td>1.0±0.02</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2.70±0.1</td>
<td>1.3-3.8</td>
<td>2.5±0.11</td>
</tr>
<tr>
<td>Lupus anticoagulant activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCT (sec)</td>
<td>75.8±5.1</td>
<td>60-120</td>
<td>90±3.4</td>
</tr>
<tr>
<td>Coagulation inhibitor assays</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombin III (IU/ml)</td>
<td>1.18±0.08</td>
<td>0.8-1.2</td>
<td>1.00±0.01</td>
</tr>
<tr>
<td>Protein C antigen (IU/ml)</td>
<td>1.23±0.05</td>
<td>0.8-1.2</td>
<td>1.00±0.01</td>
</tr>
<tr>
<td>Protein C (Protac) (IU/ml)</td>
<td>1.22±0.07</td>
<td>0.8-1.2</td>
<td>1.00±0.01</td>
</tr>
<tr>
<td>Protein S (free) (IU/ml)</td>
<td>0.91±0.04</td>
<td>0.7-1.5 for males</td>
<td>1.00±0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5-1.3 for females</td>
<td></td>
</tr>
</tbody>
</table>

Results are mean±SEM. APTT, activated partial thromboplastin time; PR, prothrombin ratio; KCT, Exner kaolin clotting time.
centration after venous occlusion. The mean tPA antigen concentration and functional activity were significantly different before and after the venous stress test ($p<0.001$).

**Discussion**

There is a male predominance in cerebral ischemia after the age of 40 years, but the sex ratio in our younger patients is almost 1:0, as previously observed. Only 36% of our patients had a identified cause or likely predisposing factor for NHCI. The most likely explanation for this small proportion is that the group is a combination of community and tertiary patient referrals. In particular, although there is a high local prevalence of rheumatic fever, the frequency of cardiac sources of emboli is likely to be underestimated because of local referral patterns.

Alcohol intoxication was the single most important precipitating factor identified. The significance of alcohol in the pathogenesis of NHCI, especially in young men, has been recognized. Alcohol may contribute to stroke by a number of mechanisms including induction of cardiac arrhythmias, enhancement of platelet aggregation, activation of the clotting cascade, or stimulation of cerebral vascular smooth muscle contraction.

In contrast to other reports in which arterial trauma due to nonpenetrating injury accounts for >20% of NHCI in young adults, trauma was responsible in only 6% of our 66 patients (17% of those with identified cause for NHCI). Strokes associated with pregnancy and the puerperium may be due to aseptic thrombosis of intracranial venous sinuses, but arterial occlusion was responsible in our two patients with this cause for NHCI.

An important feature of our study is the large proportion of patients (64%) in whom the etiology of NHCI cannot be identified after appropriate evaluation. Although a number of women in this group were taking OC, their proportion (34% of those in the reproductive age group) is the same as that estimated from National Drug and Department of Statistics information. It is unclear if young women taking low-dose estrogen OC are at increased risk of NHCI in the absence of coexisting risk factors. We were unable to implicate a preceding viral infection as an important causative factor. Paradoxical embolus, via a PFO, may be an unrecognized mechanism of NHCI.

A wide variety of coagulation abnormalities have been identified as potential risk factors for NHCI, but none has been convincingly demonstrated as being causative in an appropriately designed study. Impaired fibrinolysis due to increased plasma levels of tPA inhibitor occurs in young survivors after a myocardial infarction and has been identified in recurrent venous thrombosis. Mettinger et al demonstrated disturbed fibrinolysis in older patients (median age 50 years) 6–16 weeks after NHCI and proposed defective release of tPA from the vessel wall as the mechanism. Similarly, Tengborn et al noted a marked decrease in the concentration of fibrinolytic activators in the vessel walls and/or decreased release of these activators in 38% of subjects with cerebral ischemia. Our results demonstrate normal fibrinolytic capacity at long-term follow-up (mean 3 years) in younger patients, suggesting that an intrinsic defect in fibrinolysis is unlikely in these individuals. Normal fibrinolysis has also been reported in one other study of patients with NHCI. The concentrations of the coagulation inhibitors proteins C and S and antithrombin III were normal in our patients. Deficiencies of all of these proteins have been identified in recurrent familial thrombosis, in which a role in pathogenesis of the thromboembolism is likely and long-term anticoagulation prophylaxis is effective in preventing repeated thrombosis. The absence of any deficiency in these proteins in our high-risk population suggests that previously reported associations may be fortuitous. The latter is particularly likely with protein C deficiency, for which the prevalence of heterozygosity is said to be as high as one in 200 asymptomatic individuals.

A single patient in our study had evidence of LA activity, a history of pulmonary embolism, and recurrent spontaneous abortion. This patient’s risk status is further complicated by concurrent OC ingestion and mild rheumatic valve disease. No other patients with acquired LA were identified at follow-up, suggesting that it is not a common cause of unexplained NHCI. Anticardiolipin antibodies have previously been associated with ischemic stroke in the absence of lupus-like anticoagulant activity, but all our patients were negative for antiphospholipid antibodies using cardiolipin as the test substrate.

The prognosis of our patients was favorable, with a mortality rate of 3% and a disability of functional importance in 22% of those patients in whom follow-up information was available. Our mortality is lower than that of other reports, but a good long-term prognosis among young adults has been noted.
Although 10 of our patients had had more than one NHCI at the time of presentation, further recurrences were rare. Prognosis did not depend on a cause for NHCI having been identified, although treatment may have influenced recurrence in those with a cardiac source of emboli.

In many patients younger than 40 years with NHCI the etiology remains uncertain but the prognosis is excellent. Disturbances of the concentrations of inhibitory and fibrinolytic coagulation proteins cannot be implicated in those patients in whom the cause is not apparent after routine inpatient investigations.

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