ETIOLOGY OF YOUNG ADULT ONSET BRAIN INFARCTION IN IRAN

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Background: Stroke in young adults causes morbidity in this socioeconomically-active age group. Etiologic frequency of ischemic stroke in young adults is different around the world. This study was conducted to determine the causes of stroke in Iranian young adults.

Methods: The study population consisted of 314,000 young adult residents in the Southern Khorasan Province, East of Iran. All the patients with stroke, admitted to Vali-e-Asr Tertiary Care Hospital, entered this study. Demographic data, clinical presentation, and investigations of consecutive patients aged 15 – 45 years, presented with ischemic stroke, were registered in Southern Khorasan Stroke Database between 2000 and 2005. All the patients underwent a standard battery of diagnostic investigations by a stroke neurologist. Etiologic classification of stroke in the patients was made based on the Practical Iranian Criteria.

Results: One hundred and twenty-four patients (60 females and 64 males) were prospectively investigated during a 5-year period. The incidence of ischemic stroke in young adults was 8/100,000 per year. Cardioembolic mechanism constituted 54% of all stroke etiologies in young adults. Rheumatic valvular heart disease was present in 32% of the patients and caused 2.5 preventable stroke cases per 100,000 young adults per year.

Conclusion: Rheumatic valvular heart disease is the most common cause and a preventable etiology of stroke in Iranian young adults.

Introduction

Stroke is mainly a disease of middle-aged and elderly population. Nevertheless, young adults are also affected by the cerebrovascular disease. Although the frequency of stroke death in young adults is lower than in general stroke population, stroke is particularly dramatic in younger patients because it affects a previously-healthy adult and sometimes leads to serious sequelae for the rest of the patient’s life. The burden is also extremely serious on family and the society. The annual incidence rate of ischemic stroke in young adults has been reported to be 2 – 12 new cases per 100,000 population per year around the globe with the highest incidence reported from Libya. Cardioembolism is probably one of the most important etiologic factors that should be ruled out first in a young adult presented with ischemic stroke. In fact, the high rate of recurrence and the possibility of avoiding this by appropriate treatment, makes cardioembolism the first etiology to determine. In the literature, cardioembolism has been found to be the cause of 10 – 40% of strokes in young adults. This variable rate could be explained by various diagnostic criteria for cardioembolism and by potential geographic variations. In fact, rheumatic valvular heart disease, which was frequent in the early 20th century in western countries, is now much more prevalent as the cause of stroke in developing countries. Stroke in young adults constitutes a challenge, because of its social impact and its various etiologic factors. This...
epidemiologic study, which to the best of our knowledge is the first one in Iran, was conducted to determine the incidence and causes of ischemic stroke in Iranian young adults, with a special attention to its cardioembolic causes.

**Patients and Methods**

A population-based study was carried out in the Southern Khorasan Province, East of Iran, with a population of 682,000, and 314,000 young adults aged 15 – 45 years (49.6% females and 50.4% males). In this province, every patient with a possible diagnosis of stroke is referred to a stroke neurologist. All the stroke patients are routinely admitted to Vali-e-Asr Tertiary Care Hospital, which is the only hospital having a neurology division in Southern Khorasan. A signed informed consent was obtained from the patient or his/her next of kin to take part in this study. Those refusing to give an informed consent were excluded from the study. Consecutive patients aged between 15 and 45 years, with varying severity of ischemic stroke were hospitalized. Demographic data, clinical presentation, and results of investigations on these patients were registered in the Southern Khorasan Stroke Database between 2000 and 2005. Diagnosis and etiologic investigations of the stroke were made by a stroke neurologist. Stroke was defined as an ischemic focal neurologic deficit that persisted for at least 24 hours. Patients with cerebral venous infarction, head trauma, and vasospasm after subarachnoid hemorrhage were excluded from the study. All the patients underwent a standard battery of diagnostic investigations, including brain computerized tomography (CT) scan, electrocardiography (ECG), serum electrolytes, complete blood count, coagulation profile, fasting blood sugar, lipid profile, duplex ultrasonography of supraaortic trunks, transthoracic Doppler, and transthoracic echocardiography. A 24-hr Holter monitoring was performed for patients with a history of syncope and/or palpitation with nondiagnostic ECG. Transesophageal echocardiography was performed in those whose transthoracic echocardiography was nondiagnostic, despite a high suspicion of cardioembolism. Three serial blood cultures were requested for any stroke patient presented with fever and heart murmur or heart valvular vegetation detected by echocardiography. Brain magnetic resonance imaging (MRI) and angiography (MRA) were performed in suspected arterial dissection, arteriovenous malformation, or aneurysm. Cardiac enzymes were measured, when history or ECG evidence of recent myocardial infarction was present. An extended coagulation profile (antithrombin III, protein C, and protein S) was requested for patients without an identifiable cause of stroke, and those who had personal or a family history of venous thrombosis. Antinuclear and anticardiolipine antibodies were checked in patients with cryptogenic stroke with personal or family history of venous thrombosis, recurrent miscarriage, thrombocytopenia, cardiac valve vegetations, livedo reticularis, or raised red cell sedimentation rate. The latest was requested in patients with suspected vasculitis.

This assessment is a standard protocol in diagnostic work-up of stroke patients and does not influence the diagnoses. In nonhospitalized young adult stroke patients, brain CT scan, blood chemistry, and lipid profile were carried out. Transthoracic echocardiography and carotid Doppler ultrasonography were performed whenever possible in this group of patients. Due to incomplete diagnostic investigations, nonhospitalized patients were excluded from this study and followed in the stroke clinic. Young adult stroke patients who died before admission or evaluation by the stroke neurologist were also excluded from the study. A history of rheumatic fever was taken and confirmed by cardiologists based on the Johns criteria; rheumatic valvular heart disease was diagnosed by transthoracic echocardiography. Etiologic diagnosis was made using the Practical Iranian Criteria (PIC). The young adult population at midpoint in the time period was picked up to represent the average population at risk.

**Results**

All the hospitalized patients signed an informed consent. Two nonhospitalized patients were found ineligible to enter the study. None of the referred patients died before admission or evaluation by the stroke neurologist. One hundred and twenty-four patients (60 females and 64 males), with a mean ± SD age of 35.74 ± 7.5 years, were investigated during a 5-year period. All these patients were citizens of the Southern Khorasan Province, East of Iran, with 314,000 young adult population.

Considering these numbers, the incidence of
ischemic stroke in the hospitalized young adults was 7.9 cases per 100,000 young adults per year. The real incidence of ischemic stroke in young adults, including two nonhospitalized patients, was 8 cases per 100,000 population per year.

Holter monitoring was done for 20%, transesophageal echocardiography for 14%, and MRI for 20% of patients. Blood cultures were performed for 8%, extended coagulation profile study for 10%, and vasculitis profile for 10% of patients.

Cardiac source of embolism was found in 67 (54%) of 124 patients. Rheumatic valvular heart disease constituted 32% (40 of 124) of stroke etiologies and 59.7% (40 of 67) of cardioembolic strokes in the Iranian young adults. Rheumatic valvular heart disease caused 2.5 stroke cases per 100,000 young adult population per year.

If we assume that the two nonhospitalized patients who were excluded from the study had rheumatic valvular disease, the maximal incidence of ischemic stroke due to rheumatic valvular heart disease would be 2.6 cases per 100,000 young adult population per year.

All 29 patients (29 of 124; 23%) with atrial fibrillation had rheumatic valvular heart disease or mechanical heart valve. Atherosclerotic etiology was present in 12 patients (12 of 124; 9.7%), seven (58%) of whom had associated large artery atherosclerotic stenosis. Thirty-five of 124 (28.2%) patients had no identifiable causes of infarction. One of our patients had left ventricular thrombus and atherosclerosis (etiologic overlap). In the cardioembolic group, 35 patients were candidates for anticoagulant therapy,

Table 1 represents the frequency of various etiologies in our young patients presenting with ischemic stroke.

**Table 1.** Frequency of various etiologies in 124 young adults with ischemic stroke in North-East of Iran.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>n</th>
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<tbody>
<tr>
<td>Rheumatic valvular heart disease (35 mitral stenosis and 5 severe mitral regurgitation), (22 with atrial fibrillation)</td>
<td>40</td>
</tr>
<tr>
<td>Mechanical heart valve (7 with atrial fibrillation)</td>
<td>9</td>
</tr>
<tr>
<td>Mitral valve prolapse with mitral regurgitation</td>
<td>7</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>3</td>
</tr>
<tr>
<td>Akinetic left ventricular segment</td>
<td>2</td>
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<tr>
<td>Left ventricular thrombus</td>
<td>1</td>
</tr>
<tr>
<td>Subacute bacterial endocarditis</td>
<td>2</td>
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<tr>
<td>(1 with aortic mechanical valve)</td>
<td></td>
</tr>
<tr>
<td>Cardiac myxoma</td>
<td>1</td>
</tr>
<tr>
<td>Patent foramen ovale with paradoxical embolism</td>
<td>2</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>12</td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>2</td>
</tr>
<tr>
<td>Migraine-induced stroke</td>
<td>5</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Uncertain (cryptogenic)</td>
<td>35</td>
</tr>
<tr>
<td>All etiologies</td>
<td>124</td>
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</table>

15 – 45-year-old adults. In an etiologic study carried out on the ischemic stroke of all age groups in eastern Iran, the cardiac source of embolism could be identified in 19.8% of patients; rheumatic valvular heart disease was the underlying cause in 46.6% of cardinal embolism. Cardiac source of embolism was found in 6 – 35% of young adult patients presented with ischemic stroke in developed countries.2 – 5 Patent foramen ovale and mitral valve prolapse are reported as potential cardiac sources of embolism in these countries.2 – 5 Cardiac source of embolism was the underlying cause in 28% of patients with valvular heart disease and atrial fibrillation. In a population-based cohort study conducted in Minnesota, the ischemic cerebrovascular events developed in 13.4% of patients with valvular heart disease and atrial fibrillation had a far stronger impact on the risk of cerebrovascular events among younger patients with valve disease.21

Surprisingly, 100% of our fibrillating young adult patients with ischemic stroke had rheumatic valvular heart disease. In a 13-year follow-up study of rheumatic valvular heart disease in Japan, cerebral emboli occurred more frequently in patients with valvular heart disease and atrial fibrillation, while cerebral emboli rarely occurred in those with sinus rhythm.22 Mitral regurgitation was the most common rheumatic valvular heart disease diagnosed in the first and second decades and the relative prevalence of rheumatic mitral stenosis increased with age in South Africa.23 Rheumatic mitral stenosis and severe mitral regurgitation constituted 52% and 7.4% of cardiac sources of embolism in our young adult patients.

**Discussion**

This is the first population-based study on the incidence and causes of ischemic stroke in young Iranian adults. The annual incidence of ischemic stroke in our population is similar to western countries, however, the distribution of etiologies is quite different. Cardiac source of embolism was found in 54% of our young adult patients with cerebral infarction and rheumatic valvular heart disease constituting 32.8% of stroke etiologies in
Linking rheumatic fever to stroke needs assessment of 314,000 subjects for rheumatic fever and rheumatic valvular disease, which includes performance of transthoracic echocardiography. This type of research is very expensive, making it impossible to do for us. During the last two decades, many technologic advances have occurred in the diagnosis and management of cardiac disease in developing countries. However, during the same period little has been accomplished with respect to prevention of rheumatic fever. Lack of a primary prevention program and ineffective antibiotics to treat group A streptococcal pharyngitis lead to a high incidence of rheumatic valvular heart disease and its cerebrovascular complications in developing countries. Clear indications for anticoagulant therapy is identified in patients with cardiac sources of embolism, however, adequate anticoagulation was achieved in only 23% of our patients eligible for the treatment. The reasons for inadequate management of cardiac sources of emboli is unknown, however, inadequacies in logistics and infrastructure may be among the contributing factors.

References