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Incidence and etiology of ischemic stroke in Persian young adults

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Background – Stroke in young adults causes morbidity in this socioeconomically active age group. The etiologic frequency of ischemic stroke in young adults differs around the world. *Methods* – The study population consisted of 314,000 'young adult' residents in Southern Khorasan province in Iran. All patients with stroke are routinely admitted to the Valie Asr tertiary care hospital. Data on patients demographics, clinical presentation and investigations of consecutive patients aged 15–45 years with ischemic stroke are registered in Southern Khorasan stroke data bank for the period March 2000 to March 2005. All patients underwent a standard battery of diagnostic investigations by a stroke neurologist. The etiologic classification of stroke in the patients was made based on the trial of ORG 10172 in acute stroke treatment (TOAST) criteria. *Results* – One hundred and twenty-four patients (60 female, 64 male) were prospectively investigated during a 5-year period. The incidence of ischemic stroke in young adults was eight cases per 100,000 people per year. Cardioembolic mechanism comprised 54% of stroke etiology in young adults. Rheumatic valvular 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 disease is the most common cause and a preventable etiology of stroke in Persian young adults.

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Stroke is mainly a disease of middle aged and elderly people. Nevertheless, young adults are also affected by cerebrovascular disease. Although the frequency of stroke death in young adults is lower than in the general stroke population (1), stroke is particularly dramatic in younger patients because it involves a previously healthy adult and sometimes leads to serious sequela for the rest of the patient's life. The burden is also extremely heavy on family and society. The annual incidence rate of ischemic stroke in young adults has been reported to be 2–12 new cases per 100,000 persons around the world (2–6) and the highest incidence was recorded in Lybia (7). Cardioembolism is probably the etiology that clinicians should rule out first in a young adult with ischemic stroke. In fact, the high rate of recurrence and the possibility of avoiding this by appropriate treatment make cardioembolism the first etiology to determine. In the literature, cardioembolism has been found to be the cause of 10–40% of stroke in young adults (8–10). This variable rate could be explained by variable diagnostic criteria for cardioembolism and by potential geographic variations (1). Actually, rheumatic valvular disease which was frequent in the in early 20th century in western countries is now a much more prevalent cause of stroke in developing countries (11). Stroke in young adults constitutes a challenge because of its social impact and the large variety of associated etiologic problems. While stroke in young adults has been described in other populations, this is the first report from Iran. This epidemiologic study was designed for determining the incidence of ischemic stroke and its etiologic subtypes in Persian young adults with special emphasis on its cardioembolic causes.

Patients and methods

This population-based study was carried out in Southern Khorasan province in Iran. The general population totaling 682000 contains 314,000 young

adults aged 15–45 years (49.6% females, 50.4% males). In this province, every patient with possible diagnosis of stroke is referred to a stroke neurologist and routinely admitted to the Valie Asr tertiary care hospital. A signed informed consent was obtained from the patient or from his/her first-degree relatives. Patients who refused informed consent were excluded from this prospective study. Consecutive patients aged 15–45 years with ischemic stroke were hospitalized. Data on demographics, clinical presentation and investigations of these patients registered in Southern Khorasan stroke data bank during the period March 2000 to March 2005 are kept in a SPSS9 software package. The diagnosis and etiologic investigations of stroke was made by a stroke neurologist. Stroke was defined as an ischemic focal neurological deficit that persisted at least 24 h (12). Patients with cerebral venous infarction, head trauma and vasospasm after subarachnoid hemorrhage were excluded. All patients underwent a standard battery of diagnostic investigations (13). This included brain computed tomography (CT), electrocardiogram (ECG), blood electrolytes, blood count and differential, coagulation profile, fasting blood sugar and lipid profile, duplex sonography of supra-aortic trunks, transcranial Doppler and transthoracic echocardiography. A 24-h Holter monitoring was obtained in patients with a history of syncope and/or palpitation with non-diagnostic ECG. Transesophageal echocardiography was performed in patients in whom transthoracic echocardiography was non-diagnostic despite high suspicion of cardioembolism. Three serial blood cultures were requested for any stroke patient with fever and heart murmur or valvular vegetation detected by echocardiography. Brain magnetic resonance imaging (MRI) and magnetic resonance angiography 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, protein S) was requested in patients without identifiable cause of stroke who had a personal or family history of venous thrombosis (13). Antinuclear and anticardiolipine antibodies were obtained in cryptogenic stroke patients with a personal or family history of venous thrombosis, recurrent miscarriage, thrombocytopenia, cardiac valve vegetations, livedo reticularis or raised sedimentation rate (13). The erythrocyte sedimentation rate was requested in suspected vasculitis patients. These differential levels of assessment is a standard protocol in diagnostic work up of stroke patients and does not influence the diagnoses (13, 14). Holter monitoring, transesophageal echocardiography and MRI were performed in 20%, 14% and 20% of the patients, respectively. Blood culture, extended coagulation profile and vasculitis profile were performed in 8%, 10% and 10% of the patients, respectively. Non-hospitalized young adult stroke patients had brain CT scan, blood chemistry and lipid profile done. Transthoracic echocardiography and carotid Doppler were performed whenever possible in this group of patients. Due to the incomplete diagnostic investigations, non-hospitalized patients were excluded from the study and followed up in a stroke clinic. Young adult stroke patients who die before admission or evaluation by stroke neurologist were excluded from the study. History of rheumatic fever was determined and confirmed by cardiologists based on Johns criteria and rheumatic valvular disease was diagnosed with transthoracic echocardiography (15). Etiologic diagnosis was made using TOAST criteria (16). Incidence is defined as the number of new cases of a disease which came into existence within a certain period of time per specified unit of population. The young adult population at midpoint in the time period was picked up to represent the average population at risk (17). In this prospective study, $3.14 \times 100{,}000$ was used as person-years denominator in the calculation of cumulative incidence rate.

Results

All hospitalized patients signed informed consent. Two non-hospitalized patients were ineligible for the study. None of the referred patients died before admission or evaluation by a stroke neurologist. One hundred and twenty-four patients (60 females, 64 males; mean age 35.74, SD 7.5) were investigated during a 5-year period. All patients were citizens of Southern Khorasan province in east of Iran with 314,000 young adult population. The incidence of ischemic stroke in hospitalized young adults was 7.9 cases per 100,000 young adult people per year.

The incidence rate was calculated as (17): $A/B = 7.89$ or 24.8/3.14 per 100,000, where A is the number of new cases of ischemic stroke within people aged 15–45 years per year; $124/5 = 24.8$ and B is the population aged 15–45 years; $314000 = 3.14 \times 100{,}000$.

The real incidence of ischemic stroke in young adults, including the two non-hospitalized stroke patients is calculated as: $A/B = 8$ or 25.2/3.14 per 100 000, where A is the whole number of new cases of ischemic stroke within people aged 15–45 years per year; $126/5 = 25.2$.

Cardiac source of embolism (CSE) was found in 54% (67/124) of the patients. Rheumatic valvular disease comprised 32% (40/124) of stroke etiology and 59.7% (40/67) of cardioembolic strokes in Persian young adults. Rheumatic valvular disease caused 2.5 stroke cases per 100,000 young adults population per year. This incidence was calculated as: $A/B = 8/3.14$ per 100,000, where A is the number of new cases of ischemic stroke due to rheumatic valvular disease within people aged 15–45 years per year ($40/5 = 8$), B is the population aged 15–45 years ($314{,}000 = 3.14 \times 100{,}000$).

Assuming that the two non-hospitalized patients excluded from the study had rheumatic valvular disease, the maximal incidence of ischemic stroke due to rheumatic valvular disease would be 2.6 cases per 100,000 young adults per year.

All 29 patients (29/124; 23%) with atrial fibrillation had rheumatic valvular disease or mechanical heart valve. Based on the TOAST criteria, atherosclerosis was present in eight patients (8/124; 6.45%) and three patients (3/124; 2.42%) had lacunar infarction. Thirty-five patients (35/124; 28.2%) had no identifiable cause of infarction. One of our patients had left ventricular thrombus and atherosclerosis (etiologic overlap).

Table 1 represents the frequency of TOAST subtypes in our 124 young adults with ischemic stroke. Table 2 illustrates the frequency of cardiogenic risk factors in 67 young adults with cardiogenic stroke.

Table 1 Frequency of TOAST subtypes in 124 young adults with ischemic stroke

Etiologic mechanism	*n*	%
Cardioembolic	67	54
Atherosclerosis	8	6.45
Other determined etiologies	10	8.1
Undetermined etiology	35	28.2
Multiple possible etiologies	1	0.8
Lacunar	3	2.4

Table 2 Frequency of cardiogenic risk factors in 67 young adults with cardiogenic stroke

Cardiogenic risk factor	*n*	%
Rheumatic valvular disease*	40	59.7
Mechanical heart valve†	9	13.4
Subacute bacterial endocarditis‡	2	2.9
Acute myocardial infarction	3	4.4
Akinetic left ventricular segment	2	2.9
Left ventricular thrombus	1	1.5
Mitral valve prolapse with mitral regurgitation	7	10.4
Cardiac myxoma	1	1.5
Patent foramen ovale with paradoxical embolism	2	2.9

*Thirty-five mitral stenosis, five severe mitral regurgitation, 22 associated with atrial fibrillation.

†Seven with atrial fibrillation.

‡One with aortic mechanical valve.

Discussion

This is the first population-based study of the incidence and causes of ischemic stroke in Persian young adults. The annual incidence of ischemic stroke in our population is similar to that observed in western countries; however, the rate of frequency of the cause is quite different (2–5). CSE was found in 54% of our young adult patients with cerebral infarction and rheumatic valvular disease comprising 32.8% of stroke etiology in the 15–45 year age group. In etiologic study of ischemic stroke of whole age groups in eastern Iran, CSE was present in 19.8% of the patients and rheumatic valvular disease comprised 46.6% of the CSE (18). CSE was found in 6–35% of young adult patients with ischemic stroke in developed counties (2–5). Patent foramen ovale and mitral valve prolapse were reported as potential CSE in these countries (19, 20). In a population-based cohort study in Minnesota, ischemic cerebrovascular events developed in 13.4% of patients with valvular disease, and atrial fibrillation had a 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 disease. In a 13-year follow-up study of rheumatic valvular disease in Japan, cerebral emboli occurred frequently in patients with valvular disease associated with atrial fibrillation; however, cerebral emboli were rarely found in cases with sinus rhythm (22). Mitral regurgitation was the most common rheumatic valvular disease 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 comprised 52% and 7.4% of CSE in our young adult patients. Transthoracic echocardiography is a diagnostic test of rheumatic valvular disease. Calculation of relative risk and odds ratio between rheumatic valvular disease and stroke is performed in cohort and case-control researches which is out of the scope of our study. This type of research has very high expenses and costs. During the last two decades, many technological advances have been made 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 (11). Lack of a primary prevention program and ineffective antibiotics to treat group A streptococcal

pharyngitis have led to a high incidence of rheumatic valvular disease and its cerebrovascular complications in developing countries.

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