Ischemic Stroke in Young Adults
Risk Factors, Subtypes, and Prognosis

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Background: Ischemic strokes occurring in patients younger than 47 years is a relatively rare event and accounts for less than 5% of all ischemic strokes in western countries.

Objective: The etiologic spectrum in younger patients and older patients differs considerably.

Methods: In this hospital case series study, we enrolled 192 patients with ischemic stroke, aged 18 to 47 years, all of whom were submitted to a diagnostic protocol. The risk factors for stroke and the distribution of stroke subtype and prognosis were studied. Modified diagnostic criteria adopted from the Trial of ORG 10172 in Acute Stroke Treatment and the Baltimore-Washington Cooperative Young Stroke Study, were used for etiologic classification.

Results: Hypertension was found to be the main risk factor (45%) followed by cigarette smoking (37%), hyperlipidemia (35.4%), diabetes mellitus (17%), and family history of stroke (18%). Hypertension, diabetes mellitus, hypercholesterolemia, and smoking were present either alone or in combination in the majority of our patients. Oral contraceptives were being taken by 25% of the women. The etiology of stroke was as follows: atherothrombosis 26.5%, cardioembolism 20%, nonatherosclerotic vasculopathies 13%, other determined causes 10%, lacunar stroke 6%, migraine 3.6%, and undetermined causes 21%.

Conclusions: Hypertension, diabetes mellitus, hypercholesterolemia, and smoking were the most common risk factors in our ischemic stroke patients between 18-47 years of age. Health care programs targeting the prevention and treatment of these factors will reduce the associated morbidity and mortality of stroke among this socioeconomically active age group.

Key Words: young stroke, risk factors, prognosis

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Stroke is one of the most important causes of disability and is the second most common cause of death worldwide.[1] Ischemic stroke occurring in patients younger than 47 years is a relatively rare event and accounts for less than 5% of all ischemic strokes in western countries.[2] Risk factors for ischemic stroke in older and young patients differ considerably with the main causes being atherosclerosis in the former and cardioembolism and arterial dissection in the latter.[3,4] In developing countries, young stroke more often occurs due to atherothrombosis.[3,4] However, in developed countries, stroke is most often occurs due to arterial dissection and cardioembolic etiologies.[5,6] Although advances in diagnostic techniques have shown new potential causes of ischemic stroke, such as patent foramen ovale (PFO), arterial dissection, and coagulopathies, it is not possible to find any cause in up to one-third of patients with young stroke.[7] This study was conducted to describe the risk factors, stroke subtypes, and prognosis in patients with young stroke.

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MATERIALS AND METHODS

This study retrospectively reviewed the records of all 18-year-old to 47-year-old patients with stroke, who were admitted to the Department of Neurology in our hospital from January 2003 to July 2009. Our hospital is the only tertiary referral center in the Trakya region of Turkey to which the majority of patients with young stroke are referred. A total of 192 consecutive young ischemic stroke patients (4.5% of 4310 ischemic stroke patients) were studied.

Risk factors, presenting symptoms, subtypes of stroke, and outcome were analyzed. Patients were included in the study if they had a confirmed eligible first-ever stroke as defined by the World Health Organization.[8] A stroke was defined according to the World Health Organization criteria as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin."[8] The stroke was confirmed by clinical assessment and/or by a computed tomography (CT) and/or magnetic resonance imaging (MRI) scan. The patients who had transient ischemic attacks, vertigo, episodes of transient global amnesia, loss of consciousness, drop attacks, and migraine with aura were excluded. The patients with cerebral infarction associated with other intracranial diseases such as sinus venous thrombosis were also excluded.

The following cerebrovascular risk factors were considered: arterial hypertension (the patient was earlier diagnosed with arterial hypertension by a clinician or systolic blood pressure was >140 mm Hg and/or diastolic blood pressure was >90 mm Hg on 2 different occasions measured after the acute stage of the stroke), diabetes mellitus (earlier diagnosis, current treatment with insulin, or oral hypoglycemic medications), smoking (>10 cigarettes/d for >6 mo before stroke), hyperlipidemia (fasting blood cholesterol value was >200 mg/dL and/or the triglyceride level was >150 mg/dL), and family history of stroke.

The other evaluated factors were atrial fibrillation, earlier myocardial infarction, heart valve disease, transient ischemic attack, and alcohol consumption. Alcohol consumption was regarded as a risk factor when a patient regularly drank alcohol at a level of ≥ 30 g/d for more than 6 months before the stroke. Assessment of the carotid arteries was made by carotid duplex and/or magnetic resonance angiography (MRA). Migraine was defined according to the International Classification of Headache Disorders.[9] Oral contraceptives were defined as a risk factor when a patient had taken such drugs during the 6 months before stroke.

Patients had standard laboratory blood tests including red blood cell and white blood cell counts, platelet count, activated partial thromboplastin time, fibrinogen, erythrocyte sedimentation rate, blood glucose level, serum urea, creatinine, electrolytes, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Patients with ischemic stroke with no obvious risk factors were further investigated with assays for protein C, protein S, antithrombin III, lupus anticoagulant, anticardiolipin antibody, antinuclear antibodies, anti-DNA, antineutrophil cytoplasm antibodies, and serologic test for HIV and syphilis. We also carried out genetic tests for coagulation factors such as the G20210A mutation in the factor II (prothrombin) gene and factor V Leiden. Cerebrospinal fluid was tested when necessary, to exclude other diagnoses.

The patients were classified into 7 categories on the basis of the modified diagnostic criteria adopted from the Trial of ORG 10172 in Acute Stroke Treatment[10] and Baltimore[11] Classification Systems for patients with young stroke described by Rasura et al.[12]

1. Atherosclerotic vasculopathy: intracranial or extracranial hemodynamically significant stenosis or a plaque with an intraluminal clot shown by angiogram or noninvasive tests.
2. Nonatherosclerotic vasculopathy: angiographic, noninvasive or other evidence of arterial dissection, vasculitis, fibromuscular dysplasia, or other specific vasculopathy.
3. Lacunar infarct: small deep brain lesions (<15 mm) on neuroimaging studies or normal imaging study and lacunar syndrome.
4. Cardiac embolism: atrial fibrillation, recent myocardial infarction (within 6 wk before stroke), akinetic cardiac segments, cardiac thrombus, valvular vegetation, prosthetic heart valve, intracardiac tumors, dilated cardiomyopathy, paradoxical embolism with deep venous thrombosis, and valvular abnormalities, PFO, and atrial septal aneurysm.
5. Other determined causes: hematologic, immunologic disorders, and coagulopathies such as thrombocythemia, polycythemia, deficiency of coagulation inhibitors, antiphospholipid antibody, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, and other documented causes of stroke not listed.
6. Migrainous stroke: when the stroke occurred during or immediately after a migraine attack.
7. Undetermined: stroke was labeled as of undetermined origin, when extensive evaluation including the above-mentioned workup, failed to find the cause.

Short-term functional outcome was defined by the modified Rankin Score (mRS), in which zero represents complete recovery and 6 represents death, on discharge from hospital.

RESULTS

We reviewed the records of 192 patients aged 18 to 47 years (4.5% of all ischemic strokes) admitted with an acute ischemic stroke during the period between January 2004 and July 2009. There were 101 (53%) male and 91 (47%) female patients with a mean age of 40.2 ± 5.7 years.

All the patients had brain CT scan and 173 (90%) patients had brain MRI and MRA. Only the patients who needed acute intensive care or who had contraindications for MRI had no brain MRI. The frequency of other diagnostic investigations was Doppler sonography in 179 (93%) patients, conventional angiography in 17 (9%) patients, transthoracic echocardiography in 159 (83%) patients, and transesophageal echocardiography in 9 patients (5%).

The most common risk factors were hypertension in 87 (45%) patients, cigarette smoking in 72 (37%) patients, hyperlipidemia in 68 (35.4%) patients, diabetes mellitus in 33 (17%) patients, family history of stroke in 34 (18%) patients, alcohol intake in 17 (9%) patients, migraine in 7 (3.6%) patients, acute myocardial infarction in 5 (2.7%) patients, and valvular heart disease in 11 patients (5.7%). Oral contraceptives were being taken by 22 women (25%).

An atherosclerotic vasculopathy of the extracranial or intracranial large arteries was detected in 51 patients (26.5%). (Nineteen patients had 50% to 70% stenosis, 23 patients had >70% stenosis, and 9 patients had occlusion.)

A high probability source of cardiac embolism was detected in 38 patients (20%) including atrial fibrillation (15 patients), PFO associated with deep venous thrombosis (2 patients), recent myocardial infarction (5 patients), valvular pathology (mitral valve stenosis in 5 patients, mitral valve prosthesis in 6 patients), infectious endocarditis (1 patient), cardiomyopathy (2 patients), atrial myxoma, and thrombus in the left atrium (2 patients).

Nonatherosclerotic vasculopathy was detected in 25 patients (13%) and the causes included cervicocerebral arterial dissection in 12 patients (5%). Nine patients had dissection of the carotid arteries and 3 patients had dissection of the vertebrobasilar system. The clinical picture was compatible with vasculitis in 13 patients (7%; 4 lupus erythematosus, 1 polyartheritis nodosa, 3 neuro-Behcet disease, 1 primary central nervous system vasculitis, and 1 vasculitis secondary to bacterial meningitis).

The other group with determined causes consisted of 19 patients (10%). Antiphospholipid antibody syndrome was present in 6 patients, lupus anticoagulant syndrome in 2 patients, deficiency of protein C and protein S in 4 patients, antithrombin III deficiency in 1 patient, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy in 2 patients, idiopathic thrombocytopenic purpura in 2 patients, and polycythemia vera in 1 patient. One patient had a postpartum stroke.

Eleven patients (6%) fulfilled the criteria for lacunar infarction. The most common risk factors in this category were hypertension, hyperlipidemia, and smoking.

Seven patients (3.5%) fulfilled the International Headache Society criteria for a probable migraine-induced stroke.

Despite all investigations, the etiology of cerebral infarction could not be determined in 41 patients (21%). We did not observe any cerebral ischemic event related to drug abuse, AIDS, or syphilis.

In addition, the patients were divided into 2 age groups (18 to 35 y and 35 to 47 y), as was done in other young stroke studies.[13] Risk factors for atherosclerosis such as diabetes ($P = 0.036$), hypertension ($P < 0.001$), and hyperlipidemia ($P = 0.02$) were significantly more frequent in the older age group, but we could not find any difference between the 2 groups for smoking ($P = 0.21$), alcohol abuse ($P = 0.49$), family history of stroke ($P = 0.2$), and cardioembolic risk factors ($P = 0.56$).

The mean duration of hospital stay was 12.9 ± 8.1 days for patients with ischemic stroke. On admission, the mean National Institute of Neurological Disorders & Stroke score was 12.7 ± 9.1 and at the end of the hospital stay the mean mRS was 2.4 ± 1.8. Seventy-three patients (38%) had a poor outcome (mRS > 2) and 119 patients (62%) had a good outcome (mRS ≤ 2), 15 patients (8%) died during the hospital stay, resulting in a case fatality rate of 8% (Table 1).

TABLE 1. Distribution of Stroke Risk Factors

Risk Factors	Patients, n (%)
Hypertension	87 (45)
Smoking	72 (37)
Hyperlipidemia	68 (35.4)
Diabetes mellitus	33 (17)
Family history for stroke	34 (18)
Alcohol intake	17 (9)
Migraine	7 (3.6)
Myocardial infarction	5 (2.7)
Valvular heart disease	11 (5.7)
Use of oral contraceptives	22 women (25% of women)
Atrial fibrillation	15 (7.8)
Patent foramen ovale with deep venous thrombosis	2 (1)
Infectious endocarditis	1 (0.5)
Cardiomyopathy	2 (1)
Atrial myxoma and thrombus in left atrium	2 (1)
Cervicocerebral arterial dissection	12 (6.2)
Vasculitis	13 (6.7)
Antiphospholipid antibody syndrome	6 (3)
Lupus anticoagulant syndrome	2 (1)
Protein C and S deficiency	4 (2)
Antithrombin-III deficiency	1 (0.5)
CADASIL	2 (1)
ITP	2 (1)
Policitemia vera	1 (0.5)

N=192 patients.

CADASIL indicates cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

DISCUSSION

The annual incidence rate of ischemic stroke in young adults has been reported to be 2 to 12 new cases per 100,000 population per year around the world.[6,12–14] Although in western countries, strokes in young patients account for approximately 5% of all strokes, in developing countries the proportion of stroke in young adults has risen from 20% to 30%.[2,15] The proportion of young ischemic strokes to all ischemic strokes in our hospital was 4.3%. Stroke incidence among various populations greatly varies and is related to the distribution of risk factors, sex, and race-ethnicity groups. Compared with earlier young stroke patient studies, our study found that the distribution of stroke among young men and women was aproximately the same (53% vs. 47%), similar to the western studies[12,16–18] but different from the studies carried out in eastern countries.[14,19] Khan et al[19] from Qatar, Nayak et al[14] from India, and Kwon et al[20] from Korea reported that ischemic stroke was more frequent in young men (respectively 80% vs. 20%, 76% vs. 24%, and 75% vs. 25%).

In this study, hypertension was found to be the main risk factor (45%), followed by cigarette smoking, hyperlipidemia, and diabetes mellitus. Hypertension, diabetes mellitus, hyperlipidemia, and smoking were present either alone or in combination in the majority of our patients. In a comparison of 201 consecutive patients with first-ever stroke due to cerebral infarction aged 15 to 55 years conducted as part of the Melbourne Risk Factor Study,[21] hypertension, diabetes mellitus, current smoking, heart disease, and long-term heavy alcohol consumption were found to be the major risk factors. Hypertension, diabetes mellitus, and current smoking were also reported as important risk factors in the Baltimore-Washington Cooperative Young Stroke Study.[22]

Cigarette smoking was found in 39% of our patients. In earlier studies, it is reported that up to one-quarter of all strokes are directly attributable to cigarette smoking.[23] The risk is consistent for all subtypes of stroke and is strongest for ischemic stroke caused by arterial atherothromboembolism.[23,24] Girot[23] reported that the relative risk of stroke due to cigarette smoking is maximal in middle age, declining with advancing years. Bhat et al[24] found a strong dose-response relationship between cigarette smoking and the risk of ischemic stroke in young women. Hyperlipidemia was found as an important risk factor (37%) for young stroke in our study. Serum lipids interact with the pathogenesis of stroke through an atherosclerosis mechanism. Albucher et al[25] found that the low HDL cholesterol was the only serum-lipid index to be associated with an increased risk of stroke in young patients. Zivkovic et al[26] also reported that hyperlipidemia and very low HDL may be associated with advanced cerebrovascular atherosclerosis and stroke. In young patients with ischemic stroke, hyperlipidemia should be considered and evaluated as a risk factor.

A positive family history of stroke (18%) was one of the common risk factors in our study. A significant genetic component underlying the occurrence of young stroke was reported in earlier studies and meta-analysis of all published twin studies on stroke.[27–29] Family history was reported as the second most common risk factor by De Silva et al[30] (18.4%) in patients with young stroke in Sri Lanka, and Rasura et al[12] found a positive family history of vascular events in 63% of patients with young stroke.

Several studies have identified migraine as an independent risk factor for ischemic stroke in young patients.[31–33] Migraine was found less common (3.6%) in our study than earlier studies.[12,32,34] In the study by Rasura et al,[12] a history of migraine was present in 26% of young patients with stroke. In the study by Camerlingo et al,[32] young patients with ischemic stroke and age-matched control participantts were compared for the history of migraine, and the history of migraine was found more common in the stroke group (22.9% vs. 10.5%, $P < 0.00001$). There is also an association between migraine and PFO; PFO is a risk factor for both migraine and stroke.[35]

The attributable risk of stroke in young women using oral contraceptives is about 1 per 200,000 woman-years.[36] Use of oral contraceptives was reported in 12% of 130 young women with stroke by Barinagarrementeria et al.[37] In this study, 25% of the women were taking oral contraceptives.

The rates for atherothrombotic infarction in young stroke range from 5% to 21%.[2,6,14] In this study, we found a higher ratio (27%) when compared with the literature. This difference may be due to the older mean age (40.2 y) of our patients. Most of the similar studies in the literature included the patients who had stroke between 14 and 45 years of age. However, we included patients 18 to 47 years of age as in the study by Rasura et al[12] from Italy. Kolominsky-Rabas et al[31] also reported that an age close to 40 years represents a transition to an etiologic distribution more similar to ischemic stroke in older patients.

Stroke was caused by lacunar infarction in 6% of our patients, and this finding was in accordance with the findings observed in earlier studies.[6,12,38] Nedeltchev et al,[6] Rasura et al,[12] and Lipska et al[38] reported similar ratios for lacunar infarction (respectively, 9%, 2.5%, and 7.5%).

The incidence of an inherited deficiency of coagulation inhibitor in our study is similar to that reported in earlier studies, all of which reported an incidence of about 4% in young ischemic strokes.[15,16] Despite the routine use of duplex

ultrasonography and MRA in our patients with young acute ischemic stroke, we found only 12 patients (5%) with arterial dissection. However, Rasura et al[12] reported a higher ratio (12%) of arterial dissection with similar neuroimaging modalities.

Earlier studies have shown that PFO has a prevalence of around 24% to 50% in stroke patients younger than 45 years.[39,40] Rasura et al[12] reported that embolism of cardiac origin represented the most common etiology accounting for 34% of young strokes and the most frequent abnormality was PFO, which was detected in 54% of possible cardioembolic patients. Although cardiac embolism was detected in 20.5% (38 patients) of our patients, we only found 2 patients with PFO. This may be because of the low frequency of transesophageal echocardiogram (TEE; 5%) carried out in our study, and this is also a limitation of our study. In the group with an undetermined cause, it was possible that some of the patients who were only studied by transthoracic echocardiogram might have been classified as a cardioembolic stroke if a TEE and contrast echo had been carried out. It is known that the detection of atrial septal abnormalities depends greatly on the experience of the echocardiographer and can be improved if TEE and contrast echo are used.[41] Kristensen et al[2] found that with additional diagnostic information, derived from advanced cardiac imaging, the proportion of undetermined etiology could be reduced from 37% to 21%.

In earlier studies, the frequency of undetermined etiology of cerebral ischemia among young adults was relatively high (31% to 62%).[5,14,16] The differences in the distribution of stroke of undetermined etiology among different reports may depend on the extent of the diagnostic evaluation. Our ratio of undetermined etiology is small (22%) when compared with earlier studies.[14,16,41] This difference may be because of the detailed diagnostic workup in our study (CT: 100%, MRI and MRA: 90%, Doppler ultrasonography: 96%, and transthoracic echocardiogram: 85%). The 1-month fatality rate of ischemic stroke in young adults has been reported to be 3.8% to 22% around the world,[3,20] and in this study the in-hospital mortality rate was 8%.

A limitation of our study is that the case findings were retrospective, making determination of the etiology more difficult. The study was hospital based rather than population based, but as our center was the only referral center in our region, our findings probably reflect the actual burden of stroke in our population.

In conclusion, hypertension, diabetes mellitus, hypercholesterolemia, and smoking were the most common risk factors in our patient population with young stroke. Health care programs targeting prevention and treatment of these factors will reduce the associated morbidity and mortality of stroke among this socioeconomically active age group. The quantification of risk factors that are likely to promote premature atherosclerosis is therefore particularly important as those identified, such as hypertension and cigarette smoking, are modifiable and thus likely to help prevent stroke.

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