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Etiologic Subtypes, Risk Factors, and Outcomes of Acute Ischemic Stroke in Young Patients

Genç İskemik İnme Hastalarında İnme Etiyolojisi, Risk Faktörleri ve Hastaların İzlemdeki Fonksiyonel Durumları

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Summary

Objective: Stroke in people aged less than 45 years is less frequent than in older patients, but has major impacts on both the individual and society. The aim of this study was to determine the etiologic subtypes of acute ischemic stroke in the young.

Materials and Methods: We reviewed the hospital records of 619 patients who were admitted with acute ischemic stroke between January 2011 and November 2014. Acute ischemic stroke in the young was defined as patients aged 45 years and under. Demographic data, the National Institutes of Health Stroke Scale (NIHSS) scores at admission and detailed investigations aimed at determining etiologic cause were recorded. Etiologic stroke subtypes were determined using the automated Causative Classification System. Modified Rankin Scale (mRS) scores were recorded in the follow-up.

Results: There were 32 (5.2%) young patients with acute ischemic stroke. The rates of hypertension, diabetes mellitus, atrial fibrillation, and coronary artery disease were significantly lower in young patients compared with patients aged more than 45 years ($p<0.05$). The mean NIHSS score at admission and hospital mortality was significantly lower in patients aged 45 years and under compared with those older than 45 years ($p=0.006$, $p=0.043$). Cardioaortic embolism was the most common etiologic stroke subtype in both groups. Other causes were significantly more frequent in the young acute ischemic stroke group compared with the older patients. The median follow-up mRS was significantly lower in patients aged 45 years and under compared with those older than 45 years ($p<0.001$).

Conclusion: Young patients with ischemic stroke have different risk factors, stroke etiology, stroke severity and prognosis compared with patients older than 45 years with the same condition.

Keywords: Young patients with ischemic stroke, risk factors, stroke etiology, stroke severity, prognosis

Öz

Amaç: İskemik inme, 45 yaşın altında yaşlı popülasyona göre daha az görülse de birey ve toplum üzerindeki etkisi büyüktür. Bu çalışmanın amacı 'İnme Merkezi'mizde, genç iskemik inme geçiren hastalarda, inme etiyolojisinin, risk faktörlerinin ve hastaların izlemdeki fonksiyonel durumlarının tespit edilmesidir.

Gereç ve Yöntem: Bu çalışmada Ocak 2011 ve Aralık 2014 tarihleri arasında akut iskemik inme nedeni ile hastanemize başvurmuş 619 hastanın dosyası incelenmiştir. Genç iskemik inme, 45 yaş altında iskemik inme geçiren hastalar olarak tanımlanmıştır. Hastaların demografik özellikleri, başvuru sırasındaki Ulusal İnme Sağlık Ölçeği 'National Institute of Health Stroke Scale' (NIHSS) skorları, inme etiyolojisine yönelik yapılmış olan ayrıntılı tetkikleri kaydedilmiştir. İnme alt tipleri, otomatize Causative Classification System kullanılarak belirlenmiştir. İzlem sürecindeki modifiye Rankin Skalası (mRS) skorları kaydedilmiştir.

Bulgular: Bu çalışmaya alınan hastaların 32'si (%5,2) 45 yaş ve altında idi. Hipertansiyon, diabetes mellitus, atriyal fibrilasyon ve koroner arter hastalığı, 45 yaş ve altındaki iskemik inmeli hasta grubunda 45 yaş üstü iskemik inmeli hasta grubu ile karşılaştırıldığında istatistiksel olarak anlamlı bir şekilde daha azdı ($p<0,05$). Genç iskemik inmeli hastaların hastaneye giriş ortalama NIHSS skoru ve hastanedeki mortalite oranı 45 yaş üstü iskemik inmeli hastalardan anlamlı olarak daha düşüktü ($p=0,006$, $p=0,043$). Her iki grupta da en sık etiyolojik inme nedeni kardiyoaortik inme idi. Sadece diğer nedenler, 45 yaş ve altı iskemik

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inme grubunda 45 yaş üstü iskemik inme grubuna göre istatistiksel olarak anlamlı yüksekti (p=0,006). Ortalama takip mRS skorları 45 yaş ve altı iskemik inmeli grupta anlamlı olarak daha düşüktü (p<0,001).

Sonuç: Bizim çalışmamızda da gösterildiği gibi 45 yaş ve altı iskemik inme hastalarının risk faktörleri, inme nedenleri, inme şiddetleri ve prognozları 45 yaş üstü iskemik inme hastalarından farklıdır.

Anahtar Kelimeler: Genç iskemik inme, risk faktörleri, inme nedenleri, inme şiddeti, prognoz

Introduction

Ischemic stroke in patients aged 45 years and under is termed as stroke in the young, and previous studies have reported the incidence rate as 3.4-11.4/100.000 (1,2,3,4,5,6,7,8). The etiologic causes and risk factors are different from the overall ischemic stroke population (7,9). Several studies have indicated undetermined causes as the most common etiologic cause, (10,11,12,13,14) but others have found cardioembolic causes to be more common (6,15,16). Risk factors include hypertension (HT), diabetes mellitus (DM), dyslipidemia (DL), and smoking (15,16,17,18,19). Stroke in young adults has better prognosis. Modified Rankin scale (mRS) scores have been reported to be 0-2 at the time of hospital discharge in 80-89% of patients (7,14,16). The objective of this study was to identify stroke etiology and risk factors, as well as functional status at follow-up in patients aged 45 years and under with ischemic stroke who were hospitalized in our stoke center.

Materials and Methods

Hospital records of 619 patients, who were diagnosed as having acute ischemic stroke and hospitalized between January 2011 and November 2014, were reviewed retrospectively. Ischemic stroke was defined as a sudden focal neurologic deficit with imaging-confirmed cerebral infarction. Transient ischemic attacks are brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction (20). Patients were divided into two groups, those aged between 18-45 years, and those aged more than 45 years. Patients with intracranial hemorrhage, subarachnoid hemorrhage, and sinus vein thrombosis were excluded from the study.

Age, sex, and medical history data including the presence/absence of stroke risk factors such as HT, DM, DL, atrial fibrillation (AF), coronary artery disease (CAD), and congestive heart failure (CHF), previous history of ischemic stroke or transient ischemic attack, and National Institutes of Health Stroke Scale (NIHSS) were recorded for all patients. In addition, results of routine laboratory examinations, computed brain tomography, and diffusion-weighted magnetic resonance imaging (MRI) were recorded for all patients.

All examinations aimed at determining the stroke etiology including vascular imaging modalities such as carotid-vertebral Doppler ultrasonography, brain-cervical computed tomography angiography, magnetic resonance angiography, and digital subtraction angiography were analyzed in detail. Additionally, transthoracic and/or transesophageal echocardiography, 24-hour rhythm Holter monitorization, levels of low density lipoproteins, C-reactive protein (CRP), and laboratory tests including

Table 1. Demographic and clinical features of study groups

	Ischemic stroke patients aged 45 years and under n=32	Ischemic stroke patients older than 45 years n=587	p
Age, years, Mean ± SD	37.7±6.1	71.2±11.3	**<0.0001**
Sex, n (%)			
Female	19 (59.4)	271 (46.2)	0.15
Male	13 (40.6)	316 (53.8)	
Risk factors			
Hypertension, n (%)	12 (37.5)	420 (71.6)	**<0.0001**
Diabetes mellitus, n (%)	4 (12.5)	179 (30.5)	**0.03**
Atrial fibrillation, n (%)	0 (0)	125 (21.3)	**0.003**
Hyperlipidemia, n (%)	5 (15.6)	153 (26.1)	0.187
CAD, n (%)	1 (3.1)	143 (24.4)	**0.006**
CHF, n (%)	2 (6.2)	68 (11.6)	0.353
Previous history of TIA, n (%)	5 (15.6)	43 (7.3)	0.087
Previous history of stroke, n (%)	4 (12.5)	102 (17.4)	0.476
CRP, mg/l	17.5±35.6	23.6±40.0	0.619
Baseline NIHSS, Mean ± SD	4.3±3.2	6.2±4.6	**0.006**
Hospital mortality, n (%)	0 (0)	67 (11.4)	**0.043**
Duration of follow-up, months, Mean ± SD (Minimum-Maximum)	5.4±7.4 (1-22)	9.8±8.4 (1-32)	**0.062**
Follow-up mRS, Mean ± SD	1.3±1.8	2.6±2.4	**<0.0001**
Follow-up mRS >3, n (%)	4 (17.4)	133 (38.4)	**0.032**
Recurrent stroke, n (%)	1 (3.1)	12 (2)	0.678

SD: Standard deviation, CAD: Coronary artery disease, CHF: Congestive heart failure, TIA: Transient ischemic attack, CRP: C-reactive protein, NIHSS: National institutes of health stroke scale, mRS: Modified Rankin scale

hypercoagulability and vasculitis markers were examined. Automatized Causative Classification System (CCS) was used to determine the etiologic type of ischemic stroke (21). In addition, the rates of recurrent stroke in follow-up, hospital mortality rates, and follow-up mRS results were recorded.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc. Chicago, Illinois, USA) version 16.0. Group rates were compared using Chi-square and mean values were compared using Student's t-test. The relationship between ischemic stroke in the young and prognosis was assessed using multiple regression analysis. The level of statistical significance was set as $p<0.05$.

Results

The study population comprised 32 (5.2%) patients aged 45 years and under and 587 (94.8%) patients aged more than 45 years. No significant difference was found in sex between the two groups (Table 1).

The patients' demographic features and risk factors are presented in Table 1. The patients with acute ischemic stroke aged more than 45 years had a statistically significantly greater risk of having HT, DM, AF, and coronary artery disease compared with the young group ($p<0.05$) (Table 1).

The mean NIHSS score at hospital admission and hospital mortality rates were significantly lower in the young patients with acute ischemic stroke compared with those aged more than 45 years ($p=0.006$, $p=0.043$). Levels of CRP were compared in both groups and no significant difference was found ($p=0.619$) (Table 1).

Etiologic subtypes of ischemic stroke by CCS in the group of patients aged 45 years and under was listed as large artery atherosclerosis (LAA) (n=7, 21.9%; extracranial internal carotid artery (ICA) stenosis (n=1), extracranial vertebral artery stenosis (n=2), intracranial ICA stenosis (n=2), middle cerebral artery stenosis (n=2)), cardio-aortic embolism (n=9, 28.1%; patent foramen ovale (PFO) (n=3), symptomatic CHF with ejection fraction lower than 30% (n=2), infective endocarditis (n=2), PFO and atrial septal aneurysm (n=1), mitral stenosis (n=1)), small vessel stenosis (n=3, 9.4%), other causes (n=6, 18.8%; primary antiphospholipid antibody syndrome (n=2), acute arterial dissection (n=1), polycythemia vera (n=1), hyperviscosity syndrome (n=1), CADASIL (n=1)), stroke due to undetermined cause (n=7, 21.9%). Cardioaortic stroke was the most common etiologic subtype in both study groups, and 'other causes' was statistically significantly more common in the young ischemic stroke group ($p=0.006$) (Table 2).

A total of 308 patients had been followed up and 22 of these were in the ischemic stroke group aged 45 years and under. The mean duration of follow-up was 5.4±7.4 months (range, 1-22 months) and 9.8±8.4 months (range, 1-32 months) in the young ischemic stroke group and over 45 years group, respectively ($p=0.062$). The mean follow-up mRS scores were significantly lower among the young patients ($p<0.0001$). No significant difference was determined between the two groups in terms of recurrent stroke rates ($p=0.678$) (Table 1).

An analysis of the relationship between ischemic stroke in the young and prognosis with multiple regression analysis revealed a significant association with lower baseline NIHSS scores (Odds ratio=2.4, 95% confidence interval (0.2-5.1), $p=0.029$).

Discussion

The incidence of ischemic stroke in the young has been reported as 3.4-11.4/100.000 in previous studies (1,2,3,4,5,6,7,8), and accordingly, we found the incidence of ischemic stroke in the young group to be 5.2% in our study.

Several studies have demonstrated that ischemic stroke in the young is more common among males (14,22), whereas other studies have identified no difference between males and females (16). In our study, we found no statistically significant difference in the rates of stroke between the male and female patients.

HT, DM, DL, and smoking have been reported to be more common findings in young patients with ischemic stroke in previous studies. However, contrary to our study, most of these studies compared these risk factors in patients with ischemic

Table 2. Etiological stroke subtypes in study groups

	Ischemic stroke patients aged 45 years and under n=32	Ischemic stroke patients aged 45 years and under n=32	p
CCS classification, (%)			
Large artery atherosclerosis	7 (21.9)	145 (24.7)	0.83
Evident	7 (21.9)	145 (24.7)	
Cardioaortic embolism	9 (28.1)	247 (42.1)	0.14
Evident	6 (18.7)	201 (33.9)	
Probable	0 (0)	6 (1.0)	
Possible	3 (9.4)	42 (7.2)	
Small vessel stenosis	3 (9.4)	29 (4.9)	0.23
Evident	3 (9.4)	27 (4.6)	
Possible	0 (0)	2 (0.3)	
Other causes	6 (18.8)	29 (4.9)	**0.006**
Evident	6 (18.8)	26 (4.4)	
Possible	0 (0)	3 (0.5)	
Undetermined cause	7 (21.9)	137 (23.3)	0.99
Unknown - cryptogenic embolism	2 (6.25)	27 (4.6)	
Unknown - other cryptogenic	4 (12.5)	67 (11.4)	
Unknown - incomplete evaluation	0 (0)	15 (2.5)	
Unclassified	1 (3.25)	28(4.8)	

CCS: Causative classification system

stroke aged more than 45 years (15,16,17,18,19). Cerrato et al. (15) investigated risk factors associated with the etiologic causes of ischemic stroke separately and concluded that HT and DL was associated with small vessel disease and that smoking was associated with both small vessel disease and LAA. Lipska et al. (19) reported that lower high density lipoprotein (HDL) levels were more common among young patients ischemic stroke compared with the general population. HT, DM, AF, and coronary artery disease were more common in our group of patients with ischemic stroke aged more than 45 years compared with the young group; however, in contrast to other studies, the patients were not compared with matched age groups.

Few studies have determined stroke severity using baseline NIHSS score at hospital admission; baseline NIHSS score was reported as 3 in these studies (16,22). Our results demonstrated that baseline NIHSS score was 4.3±3.2 (0-12) in young patients ischemic stroke, and this figure was significantly lower than that of those aged more than 45 years (p=0.006).

CCS was preferred in our study for the etiologic classification of ischemic stroke in the young; TOAST has been used in previous studies.

Several studies have reported cardioembolism as the most common cause of ischemic stroke in the young (6,16). Consistent with these findings we found cardioembolic stroke to be the most common cause of ischemic stroke both in the young and those aged more than 45 years. Cardioembolic stroke was most frequently associated with PFO in the young, and AF in patients aged more than 45 years. However, other studies have reported lower rates for cardioembolic causes. This contradiction stems from the fact that these latter studies classified potential

Table 3. Etiologic stroke causes in the young reported in studies published in peer-reviewed national journals

	Criteria for ischemic stroke in the young/groups	Number of patients	Female/ Male	Risk factors	Results
Işıkay et al. (25)	Aged 45 years and under Group 1; 18-30 Group 2; 31-45	11 hemorrhagic strokes 89 ischemic strokes	56/44	HT 34% DM 10.2% HL 31.8% Smoking 48.3% Alcoholism 5.7% Family history 15.9% Migraine (1.1%) Pregnancy (6.5%) Oral contraceptive use (6.5%)	Large vessel disease + Cardioembolic stroke (40.4%) Cardioembolic stroke (24.7%) Other causes (15.7%) Undetermined cause (19.1%)
Şenol et al. (26)	Aged 50 years and under Group 1; 16-40 Group 2; 41-45 Group 3; 46-50	70 ischemic strokes	25/45	HT (40%) DM (17.1%) HL (15.7%) Smoking (18.6%) Cardiac disease (22.9%)	Large vessel disease (%9%) Cardioembolic stroke (%23%) Small vessel disease (%3%) Other causes (23%) Undetermined cause (41%)
Demir et al. (27)	17-45 years	32 ischemic strokes	18/14	HT (6.25%) HL (3.12%) Smoking (21.9%) Obesity (6.25%) Oral contraceptive use (3.12%) Migraine (3.12%)	Atherosclerotic vessel disease (28%) Cardiac originated embolus (21.9%) Other determined causes (18.8%) Non-atherosclerotic vessel disease (15.6%), Undetermined causes (12.5%) Small vessel disease (0.3%)
Acar et al. (28)	17-45 years	53 ischemic strokes	30/33	HT (34%) HL (24.5%) DM (11.3%) Obesity (11.3%) Smoking (11.3%) Alcohol (1.1%) Oral contraceptive use (1.1%)	Large vessel disease (32.1%) Cardioembolic stroke (22.6%) Other causes (20.8%) Undetermined causes (5.7%)
This study	18-45 years	32 ischemic strokes	19/13	HT (37.5%) DM (12.5%) HL (15.6%) CAD (3.1%) CHF (6.2%)	Large vessel disease (21.9%) Cardio-aortic embolism (28.1%) Small vessel disease (9.4%) Other causes (18.8%) Undetermined causes (21.9%)

HT: Hypertension, DM: Diabetes mellitus, HL: Hyperlipidemia, CAD: Coronary artery disease, CHF: Congestive heart failure

cardioembolic causes of stroke including PFO and atrial septal aneurysm (ASA) among undetermined causes of stroke. However, TOAST classification also lists these as causes of cardioembolic stroke with moderate risk, and classifies as cardioembolic stroke if no other cause can be identified (23).

Large artery atherosclerosis has been identified as the second most common cause of ischemic stroke in both groups. The high frequency of this entity among young patients might be associated with the comparable rates of hyperlipidemia in both groups.

'Other causes' has been listed as the second most common cause in several studies (7,10,11,13,14,16), whereas other studies have listed this as the third most common cause (6,15). In our study, 'other causes' ranked fourth in frequency; among these, primary antiphospholipid antibody syndrome was the most common. However, several studies have found acute arterial dissection to be the most common of all 'other causes' (13,14). This difference might be explained by the analysis of only hospitalized patients with stroke in our study.

Stroke due to undetermined causes has been reported to be more common in several studies. Moreover, it has been indicated as the most common cause in some studies (7,10,11,12,13,14,24), probably due to the lack of performance of adequate etiologic examinations.

Hospital mortality rates have been reported as 0-4.1% in previous studies (11,14,16). In our study, the hospital mortality rate was 0%.

The rate of young patients with ischemic stroke with a follow-up mRS score of 0-2 has been reported as 68-89% (7,8,11,14,16). In our study, the mean follow-up mRS score in the young patients was 1.3±1.8 and this was significantly lower than that of those aged more than 45 years ($p<0.001$). On the other hand, 82.6% of our patients had follow-up mRS <3 ($p=0.032$). The fact that baseline NIHSS scores were significantly lower among young patients with ischemic stroke compared with patients aged more than 45 years might explain the lower follow-up mRS scores in these patients.

Nedeltechev et al. (11) reported recurrent stroke in 15 out of 21 patients with follow-up. In our series, 22 patients had attended follow-up and only one of these had experienced recurrent ischemic stroke. No significant difference was found between the two groups.

Etiologic causes of ischemic stroke in the young have been examined in studies published in peer-reviewed Turkish national journals (25,26,27,28). These studies have listed risk factors associated with ischemic stroke in the young as HT, DM, HL, smoking, alcohol, oral contraceptive use, and obesity. HT, DM, and hyperlipidemia risk factors were also observed in our study population. However, smoking, alcohol, and oral contraceptive use had not been questioned in our population. Şenol et al. (26) demonstrated cardioembolic stroke as the most common cause in line with both the literature and our study. On the other hand, LAA has been identified as the most common cause in two other studies (Table 3) (27,28).

Our study had certain limitations including its retrospective and single-center design, inclusion of only hospitalized patients, the low number of patients attending follow-up, lack of smoking data, and short duration of follow-up. Nevertheless, detailed examinations had been performed in all patients to define the etiologic cause.

Consequently, the results of our study demonstrated that the risk factors, causes, severity and prognosis of ischemic stroke were different in patients aged 45 years and under compared with patients older than 45 years.

Overall, prognosis is better among young patients with ischemic stroke when hospital mortality rates, follow-up mRS scores, and recurrent stroke rates are considered. Identification of etiologic causes of stroke as well as treatment of risk factors is important to provide appropriate treatment and prevent recurrence.

Authorship Contributions

Ethics Committee Approval: This study was approved by the Ethics Committee of Ankara University. Informed Consent: Informed consent was not obtained from our patients due to the retrospective nature of our study. Concept: Canan Togay Işıkay, Mine Hayriye Sorgun, Design: Canan Togay Işıkay, Mine Hayriye Sorgun, Data Collection or Processing: İnci Şule Özer, Sefer Rzayev, Müge Kuzu, Sabiha Tezcan, Volkan Yılmaz, Çağrı Ulukan, Hafize Çotur, Anwar Rawandi, Analysis or Interpretation: Mine Hayriye Sorgun, Literature Search: İnci Şule Özer, Writer: İnci Şule Özer, Mine Hayriye Sorgun, Peer-review: Internal peer-reviewed. Conflict of Interest: Authors declare no conflicts of interest regarding this manuscript. Financial Support: Our study has not received financial support from any institution or person.

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