

ORIGINAL ARTICLE

ÖZGÜN ARAŞTIRMA

ETIOLOGY AND RISK FACTORS IN THE YOUNG PATIENTS WITH ISCHEMIC STROKE

Anwar RAWANDI, Mine Hayriye SORGUN, Sabiha TEZCAN AYDEMİR, İnci Sule OZER, Sefer RZAYEV, Muge KUZU KUMCU, Volkan YILMAZ, Cagri ULUKAN, Hafize COTUR, Canan TOGAY ISIKAY

Ankara University Faculty of Medicine, Department of Neurology, Ankara, TURKEY

ABSTRACT

INTRODUCTION: Despite the lower frequency in the young than the older population, ischemic stroke has a significant impact on the patients and their families, and the society. In this study, ischemic stroke patients under the age of 50 years registered in our stroke database were compared with elderly patients in terms of risk factors and etiologic classification. Furthermore, ischemic stroke etiology with emphasis on uncommon causes in the young population was evaluated.

METHODS: In this study, we retrospectively reviewed the data of 619 patients who were admitted with acute ischemic stroke to our hospital between January 2011 and November 2014. The patients were divided into two groups as young ischemic stroke group (patients under the age of 50) and the others with the age of ≥ 50 years. All registered demographic, clinical and paraclinical data of the patients were evaluated.

RESULTS: Thirty-two (5.2%) patients were under 50 years of age and 587 (94.8%) were ≥ 50 years of age. As vascular risk factors, hypertension, diabetes mellitus, atrial fibrillation, and coronary artery disease were found to be significantly higher in the ≥ 50 age group ($p < 0.05$). Patent foramen ovale as a risk factor of stroke was significantly more frequent in the young group. In terms of stroke etiology, cardioembolic causes were the most common in both age groups, but the etiologic subgroup of uncommon causes was found to be more frequent in the younger population.

DISCUSSION AND CONCLUSION: In our study, the risk factors and etiologic subgroups of stroke in patients younger than fifty years were found different from those in older patients. The relatively higher frequency of uncommon causes of ischemic stroke in the young population should be considered in etiology research and treatment strategies.

Keywords: Ischemic stroke, risk factors, stroke etiology, young stroke.

Address for Correspondence: Anwar Rawandi MD, Ankara University Faculty of Medicine, Department of Neurology, Ankara, Turkey.

Phone: 0312 595 60 00

E-mail: ctogay@yahoo.com

Received: 20.03.2020

Accepted: 22.04.2020

ORCID IDs: Anwar Rawandi 0000-0001-6297-436X, Mine Hayriye Sorgun 0000-0003-2370-7319, Sabiha Tezcan Aydemir 0000-0002-1288-4232, İnci Sule Ozer 0000-0001-7051-8516, Sefer Rzayev 0000-0003-2172-3470, Muge Kuzu Kumcu 0000-0002-7191-5000, Volkan Yilmaz 0000-0001-8439-8340, Cagri Ulukan 0000-0002-2952-4380, Hafize Cotur 0000-0002-5588-7994, Canan Togay Isikay 0000-0001-6256-9487.

This article should be cited as following: Rawandi A, Sorgun MH, Tezcan Aydemir S, Ozer IS, Rzayev S, Kuzu Kumcu M, Yilmaz V, Ulukan C, Cotur H, Togay Isikay C. Etiology and risk factors in the young patients with ischemic stroke. Turkish Journal of Cerebrovascular Diseases 2020; 26(1): 126-132. doi: 10.5505/tbdhd.2020.70298

İSKEMİK İNME Lİ GENÇ HASTALARDA ETYOLOJİ VE RİSK FAKTÖRLERİ

ÖZ

GİRİŞ ve AMAÇ: İskemik inme genç popülasyonda ileri yaşa göre daha az görülmele birlikte hasta, hastaların aileleri ve toplum üzerinde ciddi bir etkisi vardır. Bu çalışmada; inme veri tabanımızda kayıtlı 50 yaş altındaki iskemik inme hastaları, daha yaşlı hastalar ile risk faktörleri ve etyolojik sınıflama açısından karşılaştırılmıştır. Ayrıca, genç popülasyondaki nadir nedenler vurgulanarak iskemik inme etyolojisi değerlendirilmiştir.

YÖNTEM ve GEREÇLER: Bu çalışmada Ocak 2011 ve Kasım 2014 tarihleri arasında akut iskemik inme nedeni ile hastanemize başvurmış ve inme veri tabanımızda kayıtlı 619 hastanın dosyası retrospektif olarak incelenmiştir. Hastalar genç iskemik inme (50 yaş altında iskemik inme geçiren hastalar) ve ≥50 yaşındakiler olarak iki gruba ayrılmıştır. Hastaların tüm kayıtlı demografik, klinik ve paraklinik verileri incelenmiştir.

BULGULAR: Hastalarımızın 32'si (%5.2) 50 yaş altında ve 587'si (%94.8) ≥50 yaş grubundadır. Vasküler risk faktörleri olarak; hipertansiyon, diabetes mellitus, atrial fibrilasyon ve koroner arter hastalığı ≥50 yaş grubunda anlamlı olarak daha fazla saptanmıştır (p<0.05). Patent foramen ovale bir inme risk faktörü olarak genç popülasyonda daha sık saptanmıştır. İnme etyolojisi açısından, her iki grupta kardiyembolik olayların en sık neden olduğu görülmüştür. Nadir nedenler etyolojik alt grubu, genç yaş popülasyonunda daha sık saptanmıştır.

TARTIŞMA ve SONUÇ: Çalışmamızda, iskemik inme risk faktörlerinin ve etyolojisinin genç popülasyonda yaşlı popülasyona göre farklı olduğu gözlenmiştir. Gençlerde iskemik inmenin nadir nedenlerinin görece yüksek sıklığı, etyoloji araştırma ve tedavi stratejilerinde dikkate alınmalıdır.

Anahtar Sözcükler: İskemik inme, risk faktörleri, inme etyolojisi, genç inme.

INTRODUCTION

Ischemic stroke is a serious health problem that is associated with high mortality and morbidity rates, with an increasing incidence. According to the American Heart Association/American Stroke Association (AHA/ASA) guidelines, ischemic stroke is defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction (1).

The global burden of stroke is dramatically increasing due to the growing size and aging of the world's population. Current epidemiological data indicate that 16.9 million people suffer a stroke each year, representing a global incidence of 258/100,000/year, with marked differences between high- and low-income countries (2). The incidence of ischemic stroke is increasing in young adults, suggesting that specific preventive interventions are needed in people younger than 50.

Many analytical epidemiological studies have significantly increased the knowledge about the risk factors for stroke. The INTERSTROKE study has provided evidence that 10 risk factors alone accounted for 88% of all strokes. These risk factors are hypertension, smoking, diabetes mellitus (DM), excessive alcohol use, psychosocial factors, cardiac causes, the apolipoprotein B (apoB)/apoA ratio, waist-to-hip ratio (WHR), malnutrition, and insufficient physical activity. Many of these risk factors are modifiable, which

suggests that efforts should be made to promote interventions that aim to reduce the risk of stroke (3).

Although there are major technological advances in ischemic stroke diagnostic techniques, current mechanisms and etiology of the stroke continue to remain unclear in a significant percentage of patients (1). Several etiological ischemic stroke classifications have emerged during the last two decades; however, their reliability and validity are not very high (4). A reliable and accurate etiological classification method is of great importance for therapeutic decisions and prognostic evaluations for patients with ischemic stroke. Currently, Trial of ORG 10172 in Acute Stroke Treatment (TOAST) and Causative Classification System (CCS) classifications are the most widely used methods (5,6). The TOAST classification system divides ischemic stroke into five subgroups: large-artery atherosclerosis, small-vessel occlusion, cardioembolism, stroke of undetermined etiology, and stroke of other determined etiology (5).

Causes of ischemic stroke in young people are different from the elderly population and rare causes come to the fore more. Identification of young stroke patients at different age groups makes it difficult to evaluate the results obtained. In the literature, the age limit for stroke in young people is considered to be 40 or 50 years old.

While subarachnoid and intracranial hemorrhages constitute 15-20% of strokes in the general population and 40-55% of young stroke patients, cerebral infarction is still the most common reason (7, 8, 9). Particularly in developing countries, the risk of developing cerebral infarction increases in young adults with classic vascular risk factors due to increased smoking and urbanization rates.

Important factors that cause stroke in young patients can be listed as early atherosclerosis, cardioembolic causes, inflammatory arterial diseases, hematological causes, vascular malformations, venous thrombosis, pregnancy related strokes, dissections, and other non-inflammatory arteriopathies.

The etiology should be determined first in patients who have had a stroke. Different treatments may be considered depending on the etiology. This study aimed to compare the patients with ischemic stroke under the age of 50 with older patients, who were registered in our stroke database, in terms of risk factors and etiological classification.

METHODS

This study was conducted in accordance with Declaration of Helsinki Ethics Standards and the study protocol was approved by Clinical Research Ethical Committee of Ankara University Faculty of Medicine, (Number: 0412416, Date: 22.02.2016).

The records of all patients over the age of 18, who were hospitalized in our clinic with the diagnosis of acute ischemic stroke between January 2011 and November 2014, were retrospectively analyzed. The records were obtained from the information management system of our hospital. Demographic information of patients, all vascular risk factors, neurological examination findings, and examination results for stroke etiology were recorded from this recording system.

Strokes were classified according to their etiology using the CCS method (https://ccs.mgh.harvard.edu/ccs_title.php) after the data were gathered. The following parameters were evaluated during the stroke examination: demographic information (age, sex, comorbidities, medication), clinical history, vascular risk factors (hypertension [HT], DM, hyperlipidemia [HL], atrial fibrillation [AF], coronary artery disease [CAD], congestive heart failure [CHF], stroke and

transient ischemic attack [TIA] history), clinical findings (National Institutes of Health Stroke Scale [NIHSS]) and test results (blood tests, electrocardiography [ECG], echocardiography [Echo], Holter, magnetic resonance imaging [MRI], magnetic resonance angiography [MRA], Doppler ultrasonography [DUS]). The patients were divided into two groups: those younger than 50 years of age and those 50 years of age and older. These groups were compared in terms of stroke risk factors and etiological stroke subgroups.

Statistical analysis was performed using SPSS version 16.0 software (SPSS Inc., Chicago, Illinois, USA). Chi-Square was used to compare the proportions of the groups and Student's t-test was used to compare the mean values. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 619 patient files were examined. Of the patients, 606 (97.9%) were seen to have stroke for the first time whereas 13 (2.1%) had recurrent stroke. Of the patients, 32 (5.2%) were under 50 years of age whereas 587 (94.8%) aged 50 years and older. In the <50 age group, 40.6% of the patients were male and 59.4% were female whereas 53.8% were male and 46.2% were female in the ≥50 age group.

Stroke etiology and risk factors of patients in two different age groups are summarized in Table I. When the ≥50 age group and the <50 age group were compared, the incidence of HT, CAD, DM, and AF was significantly higher in individuals with the age of 50 years or more. (HT; $p<0.001$, CAD; $p=0.006$, DM; $p=0.03$, AF; $p=0.003$). On the other hand, the incidence of patent foramen ovale (PFO) was significantly higher in the <50 age group ($p<0.001$).

Rare causes of stroke in the groups are shown in Table II. Rare causes were identified in 29 individuals in the ≥50 age group and in six individuals in the <50 age group in terms of stroke etiology. In the ≥50 age group, rare causes of stroke were found to be cancer in 11 (37.9%) patients, essential thrombocytosis in seven (24.1%) patients, polycythemia vera in two (6.8%) patients, cerebral vasculitis in three (10.3%) patients, cerebral aneurysm in three (10.3%) patients, acute arterial dissection in one (3.4%) patient, Sneddon syndrome in one (3.4%) patient, and homocystinuria in one (3.4%) patient.

Table I. Stroke etiology and risk factors in two groups.

	≥50 age group (n= 587, 94.8%)	<50 age group (n= 32, 5.2%)	p value
Stroke subtype (number-%)			
Large artery atherosclerosis	145 (24.7)	7 (21.9)	0.83
Cardio-aortic embolism	247 (42.1)	9 (28.1)	0.14
Small artery occlusion	29 (4.9)	3 (9.4)	0.23
Rare causes	29 (4.9)	6 (18.8)	0.006*
Undetermined	37 (23.3)	7 (21.9)	0.99
Risk factors (number-%)			
Hypertention	420 (71.6)	12 (37.5)	<0.001*
Diabetes Mellitus	179 (30.5)	4 (12.5)	0.03*
Hyperlipidemia	153 (26.1)	5 (15.6)	0.187
Atrial fibrillation	125 (21.3)	0 (0)	0.003*
Coronary artery disease	143 (24.4)	1 (3.1)	0.006*
Congestive heart failure	68 (11.6)	2 (6.2)	0.353
Cancer	45 (7.7)	1 (3.1)	0.34
History of stroke	102 (17.4)	4 (12.5)	0.476
Temporary ischemic attack history	43 (7.3)	5 (15.6)	0.087
Myocardial infarction in the past month	16 (2.7)	0 (0)	0.344
Patent foramen ovale	27 (4.6)	7 (21.9)	<0.001*

* P<0.05

Table II. Rare causes of ischemic stroke in two groups.

≥50 age group	<50 age group
Cancer-related stroke (n=11)	Primary antiphospholipid antibody syndrome (n=2)
Essential Thrombocytosis (n=7)	Acute arterial dissection (n=1)
Polycythemia vera (n=2)	Polycythemia vera (n=1)
Cerebral Vasculitis (n=3)	Essential thrombocytosis (n=1)
Cerebral aneurysm (n=3)	CADASIL (n=1)
Acute arterial dissection (n=1)	
Sneddon syndrome (n=1)	
Homocystinuria (n=1)	

CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

When the rare causes of stroke in the <50 age group were examined, the stroke was seen to be caused by essential thrombocytosis in one (16.6%) patient, polycythemia vera in one (16.6%) patient, acute arterial dissection in one (16.6%) patient, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in one (16.6%) patient, and primary antiphospholipid syndrome in two (33.2%) patients.

DISCUSSION AND CONCLUSION

According to the National Survey of Stroke statistics, 3.7% of all strokes occur in individuals aged 15–45 (10). Studies carried out in developing countries have shown that approximately 2.8 to 7.6% of patients who have had a stroke are younger than 45 years of age (11). In the present study, the rate of the patients (<50 years) who had a stroke at a younger age was 5.2%, which is compatible with the literature.

In the present study, cardioembolic stroke has been found to be the most frequently observed

etiologic factor in both groups. In the literature, the most common cause for all age groups is the undetermined etiology subgroup (12,13,14). According to the results in the literature, observing such a difference may have resulted from detailed studies on the etiology of stroke in our center. The proportion of patients with small vascular disease in our database has been found to be lower than the literature. The fact that most patients in this group undergo outpatient treatment and are not registered in our database because of the mild clinical picture may explain this difference.

There has been a significant difference between the two groups in terms of the presence of HT, DM, AF, CAD, and PFO. The incidence of HT has been found to be higher in the older patient group. The incidence of HT has been found to be higher in the older patient group Nevertheless, HT has also been the most common vascular risk factor in the younger age group in the present study. This result is partially compatible with the literature. When looking at the risk factors of stroke in the younger age group, hypertension has

been determined to be the most common risk factor in some studies (14,16) whereas there are also studies reporting that it follows other risk factors (12,15). In some studies, dyslipidemia, smoking, and physical inactivity have been reported to be among the leading risk factors (13,15). In the present study, HT has been found to be the most common risk factor in the group consisting of younger patients, followed by PFO. This is a retrospective study and smoking, alcohol use, and physical activity information could not be obtained since they are not recorded in the database where stroke patients are registered. Thus, this may have led to different results.

The presence of DM has been found to be significantly higher in the ≥ 50 age group. Since the prevalence of DM is known to increase with the advancing age, this finding is compatible with the expected results. There are studies reporting the incidence of DM as 2–10% (12) and 5–20% (17) in young population with stroke. This rate has been found to be 12.5% and is compatible with the literature.

Atrial fibrillation has been observed to be more common in the ≥ 50 age group. In general, the frequency of AF increases with the advancing age and its prevalence has been reported to be 0.1% in the population aged < 55 years. The presence of AF has been reported to be the most common cause of stroke in the young population and cardioembolic stroke in the general population (16). However, none of the patients in the younger age group had AF in the present study.

The prevalence of CAD, which is one of the risk factors for stroke, has been found to be significantly higher in the old age group in the present study. In the literature, the prevalence of CAD in stroke patients has been reported to be 22% at an advanced age and 1–2% at < 45 years of age (18,19). These rates have been determined as 24% and 3.1%, respectively in the present study and are similar to the findings in the literature.

We have found the prevalence of PFO higher in the younger age group. The prevalence of PFO in the general population has been reported to be about 25% in the literature. Its incidence has been reported to be 25–30% in young stroke patients and 30–50% in the cryptogenic ischemic stroke group (12). In a review, the prevalence of PFO has been reported to be significantly lower in stroke patients at an advanced age compared to stroke

patients at a younger age (17). In the present study, PFO prevalence has been found to be higher in young patients, however, it has been found lower in both groups (24% in young adults and 4% in older age group) compared to the literature. In practice, the presence of PFO is generally investigated in patients with cryptogenic stroke while investigating the etiology of ischemic stroke. Therefore, the presence of PFO has not been thoroughly investigated in all patients included in this study (with transesophageal Echo or bubble test). This may have led to a lower PFO rate compared to the literature.

Rare etiological causes (other causes) have been found to be more common in younger stroke patient group. The prevalence of rare causes is 18.8% in the younger patient group and about four times frequent than that of the ≥ 50 age group. This is an expected finding and compatible with the literature (12,13,14).

The rare causes in young stroke patients in the present study have been found to be primary antiphospholipid syndrome, acute arterial dissection, polycythemia vera, essential thrombocytosis, and CADASIL. In a review, the most common rare causes in this age group have been reported as non-inflammatory arteriopathies (arterial dissection, reversible vasoconstriction syndrome), inflammatory arteriopathies (arteritis), and prothrombotic states (17). On the other hand, arterial dissection, fibromuscular dysplasia, vasculitis (Churg-Strauss, Wegener, Behçet's disease), infectious causes (syphilis, Chagas disease), and hematological conditions (paroxysmal nocturnal hematuria, leukemia, sickle cell anemia) have been reported as the most common rare causes seen in patients with ischemic stroke in a different review (16).

In our study, the rare causes of stroke in patients aged ≥ 50 years were as follows: cancer related stroke, essential thrombocytosis, polycythemia vera, cerebral vasculitis, cerebral aneurysm, acute arterial dissection, Sneddon syndrome, and homocystinuria. In the literature, rare causes of ischemic stroke in the general population have been listed as hematological disorders (essential thrombocytosis, polycythemia vera, cigarette-related polycythemia, acute lymphoblastic leukemia, acute non-lymphoblastic leukemia, Waldenstrom macroglobulinemia, lymphocytic lymphoma, aplastic anemia, IgA

lambda myeloma, primary anti-phospholipid syndrome), infectious conditions (HIV infection, syphilitic, meningococcal and pneumococcal meningitis), migraine, secondary to venous thrombosis (septic thrombophlebitis, oral contraceptives, Protein C deficiency, Behçet's disease, breast cancer, abuse of sympathomimetics, idiopathic), inflammatory vascular disorders (giant cell vasculitis, SLE, sarcoid angiitis) and others (arterial dissection, tumor-related arterial compression, aneurysm induced embolism, Moyamoya disease, cocaine abuse, homocystinuria) (20).

We were not able to investigate the risk factors such as cigarette/alcohol use, physical inactivity, and obesity since patients' records were retrospectively analyzed. This situation has affected the outcomes of our study and made them difficult to interpret. We could not compare our results with other studies in the literature because the number of patients in the young age group was small and rare causes were observed only in six patients. Other weaknesses of this study were its retrospective design, being conducted in a single center, and including only the patients who were hospitalized.

In conclusion, this study has shown that the risk factors and etiology of ischemic stroke differ between young adults and the elderly population. The prevalence of HT, DM, AF, and CAD risk factors were significantly higher in the ≥ 50 age group, as expected, whereas the prevalence of PFO as a risk factor was higher in the younger age group. Considering the etiological subgroups of ischemic stroke, the prevalence of rare causes in the young population was significantly higher than in the older population. These results are compatible with the literature and indicate that there is a need for a different approach in the treatment and prophylaxis of ischemic stroke in the young population.

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Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethical Committee of Ankara University Faculty of Medicine (Number: 0412416, Date: 22.02.2016).

Informed Consent: Informed consent was not obtained from

the patients because the study was a retrospective data analysis.

Copyright Transfer Form: Copyright Transfer Form was signed by all authors.

Peer-review: Internally peer-reviewed.

Copyright Transfer Form: Copyright Transfer Form was signed by all authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Authorship Contributions: Surgical and Medical Practices: AR, MHS, STA, İŞÖ, SR, MKK, VY, ÇU, HÇ, CTI, Concept: AR, MHS, STA, İŞÖ, SR, MKK, VY, ÇU, HÇ, CTI, Design: AR, MHS, STA, İŞÖ, SR, MKK, VY, ÇU, HÇ, CTI, Data Collection or Processing: AR, MHS, STA, İŞÖ, SR, MKK, VY, ÇU, HÇ, CTI, Analysis or Interpretation: AR, MHS, STA, İŞÖ, SR, MKK, VY, ÇU, HÇ, CTI, Literature Search: AR, MHS, STA, İŞÖ, SR, MKK, VY, ÇU, HÇ, CTI, Writing: AR, MHS, STA, İŞÖ, SR, MKK, VY, ÇU, HÇ, CTI.

Financial Disclosure: The authors declared that this study received no financial support.