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The Most Common Etiologies in Young Cryptogenic Strokes and Their Relationship with RoPE Score

Genç Kriptojenik İnmelerde En Sık Görülen Etyolojiler ve RoPE Skoru ile İlişkileri

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ABSTRACT

Objectives: This study was designed to determine the underlying etiologies and their relationship with the Risk of Paradoxical Embolism (RoPE) score in young cryptogenic stroke patients.

Methods: In the study, among 1434 patients who were treated with a diagnosis of transient ischemic attack/ischemic stroke in our neurology clinic between May 2021 and May 2023, 121 patients between the ages of 18-50 were evaluated retrospectively. The demographic characteristics of the patients, past medical history, admission and 24-hour National Institutes of Health Stroke Scale (NIHSS) scores, infarct localization, hospital stay, and 90-day modified Rankin score (mRS) were evaluated. RoPE scores were calculated for 48 patients who had no history of chronic disease and were considered to have cryptogenic stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. The study protocol was approved by the hospital ethics committee (2023/84). Artificial intelligence was not used in the article.

Results: The average age was 38.90, and 66.7% of the patients were male. The mean baseline NIHSS score was 4.65, and the most common stroke location (64.6%) was the MCA irrigation area. The most common etiology was Patent Foramen Ovale (PFO) with a rate of 37.5%. RoPE score was grouped as >7 and <7, and the relationship between TOAST etiology, NIHSS at admission and 24th hour NIHSS, duration of hospitalization, and Day 90 mRS and PFO closure was evaluated (p=0.381, p=0.509, p=0.447, p=0.591, p=0.884, p=0.500).

Conclusion: In our study, the most common cause detected in patients with a RoPE score > 7 was PFO. No significant relationship was found between RoPE score and PFO closure. No significant relationship was found between causes other than PFO and RoPE score. Although it is thought that evaluation with the RoPE score may be effective in cryptogenic strokes, further studies are needed to detect etiologies other than PFO.

Keywords: Cryptogenic stroke; RoPE score; Young stroke.

ÖZET

Amaç: Bu çalışma, genç kriptojenik inme hastalarında altta yatan etyolojileri ve bunların Risk of Paradoxical Embolism (RoPE) skoru ile ilişkisini belirlemek için tasarlandı.

Yöntem: Çalışmada, Mayıs 2021 - Mayıs 2023 tarihleri arasında nöroloji kliniğimizde geçici iskemik atak (GİA) / iskemik inme tanısı ile tedavi gören 1434 hasta arasından, 18-50 yaş aralığındaki 121'i retrospektif olarak gözden geçirildi. Hastaların demografik özellikleri, geçmiş tıbbi öyküleri, başvurudaki ve 24. saat National Institutes of Health Stroke Scale (NIHSS) skorları, enfarkt lokalizasyonu, hastanede kalış süresi ve 90. gün modifiye Rankin skoru (mRS) değerlendirildi. Özgeçmişlerinde kronik hastalık öyküsü olmayan, Trial of Org 10172 in Acute Stroke Treatment (TOAST) sınıflamasına göre kriptojenik inme kabul edilen 48 hasta için RoPE skorları hesaplandı.

Çalışma protokolü hastane etik kurulu (2023/84) tarafından onaylandı.

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Bulgular: Yaş ortalaması 38.90 olup hastaların %66.7'si erkekti. Başlangıç NIHSS skoru ortalama 4.65, en sık inme lokalizasyonu (%64.6) MCA sulama alanıydı. Etyolojide en sık %37.5 oranında Patent Foramen Ovale (PFO) saptandı. RoPE skoru >7 ve <7 olarak gruplandırılarak TOAST etyolojisi, başvurudaki NIHSS ve 24. saat NIHSS, hastanede yatış süresi ve 90. gün mRS ve PFO kapatılması arasındaki ilişki değerlendirildi (p=0.381, p=0.509, p=0.447, p=0.591, p=0.884, p=0.500).

Sonuç: Çalışmamızda RoPE skoru >7 olan hastalarda en sık saptanan neden PFO idi. RoPE skoru ile PFO kapatılma arasında anlamlı ilişki bulunmadı. PFO dışındaki nedenler ile RoPE skoru arasında anlamlı ilişki bulunmadı. Kriptojenik inmelerde RoPE skoru ile değerlendirmenin etkili olabileceği düşünülmekle birlikte PFO dışı etyolojileri saptama açısından ileri çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Genç inme; Kriptojenik inme; RoPE skoru.

The official definition of youth stroke generally covers those between 18 and 50.[1] Cerebrovascular disease in young adults is reported to occur around 6–26 per 100,000 people worldwide. Although survival after stroke is high in young patients, survivors may face complications such as recurrent stroke, neuropsychiatric problems, and epileptic seizures at older ages. It also requires more extensive investigation because the causes of stroke vary more among younger adults than among older adults.[2]

Cryptogenic stroke (CS), which represents approximately 20–25% of all ischemic strokes, continues to occur despite basic research (including arterial imaging, electrocardiography (ECG), transthoracic echocardiography (ECO), 24-hour rhythm holter, lipid profile, and basic laboratory studies that include risk factors such as hemoglobin A1c [HbA1c]). It describes the subset of ischemic strokes for which the cause cannot be found. There are many putative mechanisms of CS, including occult structural heart lesions, paroxysmal atrial fibrillation (AF), hypercoagulopathy state, or diagnosed/undiagnosed malignancy.[3–6]

Since the 10-year risk of recurrence in CS is estimated to be as high as 30%, studies focusing on unraveling the causal relationship are ongoing to reduce this rate.[5,7] Based on the fact that many of the proposed CS mechanisms are embolic and on studies showing similarities in thrombus composition between cardioembolic and CS, the concept of embolic stroke of undetermined source (ESUS) has been proposed to identify CS that may require systemic anticoagulation.[3,6,8] In a secondary analysis of randomized clinical trial data, most recurrent strokes after ESUS were embolic and their source was undetermined. A more comprehensive investigation to identify the embolic source is important for an effective antithrombotic strategy. The effectiveness of secondary prevention strategies generally depends on the accurate and timely identification of the underlying cause.[6]

In the article published in the American Academy of Neurology journal in 2013, which evaluated the data of 12 studies, a 10-point Risk of Paradoxical Embolism (RoPE) scoring was recommended. According to this scoring system, cases with cortical stroke at a young age and without vascular risk factors were found to have a high-risk score.[9] Given this information, our study was designed to determine the underlying etiologies and their relationship with the RoPE score in young CS patients without vascular risk factors.

Methods

Our hospital, which has been actively working as a stroke center since 2016, performs brain tomography (CT) to distinguish ischemic and hemorrhagic stroke along with basic blood tests for every patient with a preliminary diagnosis of stroke who applies to the emergency department. CT Angiography (CTA) is performed on patients whose creatinine level is normal after hemorrhagic strokes are excluded. Magnetic resonance (MR) imaging is performed in patients with suspected ischemia, provided that acute stroke treatment is not delayed.

Information about stroke patients admitted to our clinic (age, gender, initial stroke severity, stroke type, lesion localization for hemorrhagic strokes, acute stroke treatment for ischemic strokes, detected etiology) is recorded in the database within the framework of the consent obtained during hospitalization. Stroke severity is expressed by the National Institutes of Health Stroke Scale (NIHSS).

Routine biochemical tests (glucose, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride), thyroid function tests, complete blood count, prothrombin time, and activated partial thromboplastin time are evaluated to determine the etiology of stroke in all patients. In the group under 50 years of age, defined as young stroke, additional tests including antiphospholipid antibodies, lupus anticoagulant, homocysteine, fibrinogen, Protein C and S, activated protein C resistance, antithrombin III, Factor V Leiden mutation, methylene tetrahydrofolate

reductase (MTHFR), and vasculitis markers (rheumatoid factor, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, complement C3 and 4) are examined.

Carotid-vertebral artery color Doppler duplex ultrasonography (CVA-USG) is performed in patients where CTA cannot be performed to determine the etiology. Full sequence cranial MR, MR venography, and digital cerebral angiography (DSA) are performed in necessary patients. ECG is taken to investigate the cardioembolic source, transthoracic ECO is performed by obtaining a cardiology opinion, and necessary patients are evaluated with 24-hour rhythm holter and/or transesophageal ECO monitoring during their hospitalization period.

With all the results, ischemic stroke patients are classified etiologically into 5 groups by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification:[1] large artery atherosclerosis,[2] cardioembolism,[3] small vessel occlusion,[4] other established etiology (e.g., arterial dissection),[5] or of undetermined origin (e.g., cryptogenic).[6]

In the study, 121 patients, aged between 18–50, among 1434 patients who received inpatient treatment with a diagnosis of transient ischemic attack (TIA)/ischemic stroke in our neurology clinic between May 2021 and May 2023, were retrospectively reviewed. Demographic characteristics and past medical history of these patients (hypertension [HT], diabetes mellitus [DM], hyperlipidemia [HL], coronary or peripheral artery disease, congestive heart failure, presence of AF, and smoking) were recorded. NIHSS scores at admission and 24th day, infarct localization, hospital stay, and 90th-day modified Rankin score (mRS) were evaluated.

48 patients who did not have a history of chronic disease in their medical history and whose cause of stroke could not be determined through etiological studies conducted according to the TOAST classification and were considered to have CS were identified. RoPE score was calculated for these patients as determined in the literature.[9] One point was awarded for each of the following: No history of arterial HT, DM, TIA/stroke, non-smoking, and cortical localization of the cerebral infarct. A score between 0 and 5 was added depending on the patient's age at the time of the ischemic event (0 for >70; 1 for 60–69; 2 for 50–59; 3 for 40–49; 4 for 30–39; 5 for 18–29) (Table 1).

The study protocol was approved by the hospital ethics committee (2023/84) and by the Declaration of Helsinki. Number (n) and percentage (%) values were used to show the distribution of individuals in demographic information such as gender, disease status, and stroke location. The suitability of the continuous variables in the study to normal distribution was evaluated graphically and with the Shapiro-Wilks test. It was determined that none of the continuous variables (except age) followed a normal distribution. Mean±SD (standard deviation) and Median (minimum–maximum) values were given to display the descriptive statistics of the variables.

Table 1. RoPE score calculation

Variable	Point
No history of hypertension	1
No history of diabetes mellitus	1
No history of TIA or stroke	1
Not smoking	1
Presence of cortical infarction	1
Age	
18-29	5
30-39	4
40-49	3
50-59	2
60-69	1
≥70	0
Total Score	

Cross tables were created to compare categorical variables according to the RoPE score classification, and number (n), percentage (%), and chi-square test statistics were given. Mann-Whitney U test was used to compare arrival NIHSS, 24th-hour NIHSS, length of stay, and 90th-day mRS values according to the RoPE score classification.

IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 programs were used for statistical analyses and calculations. The statistical significance level was accepted as $p<0.05$.

Results

The average age of the individuals in the study population was 38.90±7.86 years, 33.3% (n=16) were female and 66.4% (n=32) were male (Table 2). Considering their medical history, none of the individuals had HT, DM, HL, coronary or peripheral artery disease, congestive heart failure, or AF. There were 29 individuals (60.4%) who smoked and 1 individual (2.1%) with migraine.

Table 2. Characteristics of the group

	n=48
Age (years)	39.90±7.86
Gender, n (%)	
Female	16 (33.3)
Male	32 (66.7)
Smoking, n (%)	
No	19 (39.6)
Yes	29 (60.4)
RoPE score, n (%)	
<7	19 (39.6)
≥7	29 (60.4)
Hospital admission time, n (%)	
< 4.5 hours	15 (31.2)
≥4.5 hours	33 (68.8)
Infarct localization, n (%)	
MCA (medial cerebral artery)	31 (64.6)
ACA (anterior cerebral artery)	1 (2.1)
PCA (posterior cerebral artery)	7 (14.6)
Brainstem	6 (12.4)
Cerebellum	3 (6.2)
Etiology, n (%)	
PFO	18 (37.5)
Internal carotid artery dissection	5 (10.4)
Vertebral artery dissection	3 (6.3)
AF	3 (6.3)
Vasculitis	2 (4.2)
Undetermined	17 (35,3)

It was determined that the RoPE score was <7 in 39.6% (n=19) of the individuals and ≥7 in 60.4% (n=29). The application time of individuals was >4.5 hours in 68.8% (n=33) and <4.5 hours in 31.2% (n=15). The mRS is 0.00±0.00, and the NIHSS average is 4.65±4.81. In stroke locations, medial cerebral artery (MCA) infarction was most frequently seen in 64.6% (n=31). Considering the stroke locations of our cases, MCA infarction was observed in 64.6% (n=31), 15 of whom were left and 16 were right, and 1 had right ACA infarction.

Etiologically, patent foramen ovale (PFO) was present in 37.5% (n=18), Internal Carotid Artery (ICA) dissection was present in 10.4% (n=5), vertebral artery (VA) dissection was present in 6.3% (n=3). AF was detected in 100 patients (n=3), other causes (antiphospholipid syndrome and vasculitis) were detected in 4.2% (n=2), and no cause was found in 35.3% (n=17). PFO was closed in 50.0% (n=9) of individuals with PFO.

Among individuals with a RoPE score <7, PFO was observed in 26.3% (n=5), ICA/VA dissection in 21%, AF in 10.5% (n=2), and no cause was found in 42.2% (n=8).

Of the individuals with a RoPE score ≥7, PFO was observed in 44.8% (n=13), ICA/VA dissection in 13.8%, AF in 3.5% (n=1), and no cause was found in 31.0% (n=9).

No statistically significant difference was detected in terms of etiology distribution according to RoPE score (p=0.381).

There was no statistically significant difference between the RoPE score and the 90th-day mRS values (p>0.05).

Discussion

Ischemic strokes can result from many different mechanisms, most of which can be easily identified following a standard diagnostic evaluation. However, in approximately 20–25% of cases, the etiology of stroke is unknown. Since the effectiveness of secondary prevention strategies generally depends on the accurate and timely identification of the underlying cause, there is a need to eliminate this clinical uncertainty.[6,8]

The official definition of youth stroke generally covers those between the ages of 18 and 50.[1] In different studies, the lower limit is taken as 15–18 years of age, and the upper limit is 45–55 years of age.[1,10] Cerebrovascular disease in young adults is reported to be around 6–26 per 100,000 people worldwide.[11,12] While juvenile stroke is common in women under the age of 35, it is thought to be more common in men between the ages of 35 and 50. Gender-specific risk factors such as pregnancy in young women of reproductive age, postpartum period, and oral contraceptive use, and the intensification of vascular risk factors in middle-aged men may cause this difference.[13,14] Although survival after stroke is high in young patients, survivors may face complications such as recurrent stroke, neuropsychiatric problems, and epileptic seizures at older ages. It also requires more extensive investigation because the causes of stroke vary more among younger adults than among older adults.[2]

The development and change of the understanding of CS over the years is the classification used (TOAST, A-S-C-O (A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause), Causative Classification System (CCS)) methods. However, even with these new structures, CS remains a diagnostic challenge.[7,15–17] Those whose source cannot be changed after a summary evaluation with

the TOAST system, which is the first and most frequently used definition, are divided into three groups: cryptogenic, incomplete evaluation, and the presence of more than one etiology.[6,8,15,17] CS comprises a heterogeneous but clinically important collection of stroke etiologies.[5] There are many putative mechanisms of CS, including occult structural heart lesions, paroxysmal AF, hypercoagulopathy state, or diagnosed/undiagnosed malignancy.[3–6] Based on the fact that many of the proposed CS mechanisms are embolic and on studies showing similarities in thrombus composition between cardioembolic and CS, the concept of embolic stroke of undetermined source (ESUS) has been proposed to define CS that may require systemic anticoagulation.[3,6,8]

In secondary analysis of randomized clinical trial data, most recurrent strokes after ESUS were embolic and of undetermined origin. It is underlined that more comprehensive research to determine the embolic source is important for an effective antithrombotic strategy.[4] On average across studies, patients with ESUS are younger and have lower initial stroke severity, lower cardiovascular risk factor burden, and lower mortality than patients with cardioembolic etiology.[18–21] According to the RoPE score, it was observed that cases with cortical stroke at a young age and without vascular risk factors had a high-risk score.[9]

14.1% of ischemic strokes in Türkiye and 11% in the world are reported under the age of fifty, and the young stroke rate in our study population was 8.4%.[22] According to the study design, the average age of 48 patients without chronic diseases was 38.90±7.86 years and 66.4% (n=32) were male. The inequality of the gender groups included in the study was explained by the evaluation of the group without chronic diseases in the study design. The average age of female individuals was 39.31 and male individuals was 38.68. The unequal gender groups included in the study were explained by the evaluation of the group without chronic diseases in the study design.

Considering the stroke locations of our cases, MCA infarction and 1 right ACA infarction were observed in 64.6% (n=31), including 15 left and 16 right. Despite studies suggesting that left hemisphere lesions can be recognized more easily and cerebral blood flow, which carries emboli less likely, is preferred more from the left side, no difference was detected between the hemispheres in Portegies et al.'s study based on cranial imaging, as in our study.[4,23–25] In our study, stroke etiologies were evaluated: PFO in 37.5% (n=18), ICA dissection in 10.4% (n=5), VA dissection in 6.3% (n=3), AF in 6.3% (n=3). Other rare causes were detected in 4.2% (n=2), and no cause was found in 35.3% (n=17).

Cardiac septal defects, especially paradoxical embolization with PFO, are a potential mechanism of stroke. Still, since this condition is so common in the general population (rates up to 25%), it may be difficult to determine the degree to which ischemic stroke is attributable to PFO.[26] In those under 60 years of age with CS, half of the patients have PFO; this rate is twice the prevalence in the general population.[26,27] The determination of the PFO rate as the highest cause in our study is compatible with this information.

Treatment options for CS patients in the presence of PFO include medical treatment with antiplatelet therapy or anticoagulation and closure of the PFO. Results from the recent CLOSE, REDUCE, and DEFENSE-PFO studies identified a subgroup of patients with CS and PFO who may benefit most from PFO closure, particularly for secondary prevention.[28–30] Guidelines recommend that PFO closure (in addition to antiplatelet therapy) be considered in patients aged 60 years and younger with apparently embolic stroke unless a comprehensive diagnostic evaluation reveals another cause.[31,32] In our study, PFO was closed in 50.0% (n=9) of the individuals with PFO, and it was not closed in 50.0% (n=9).

It was determined that the RoPE score of 39.6% (n=19) of the individuals was <7, and 60.4% (n=29) was ≥7. No statistically significant difference was found in terms of etiology (PFO, ICA or vertebral artery dissection, AF, undetermined cause) distribution according to the RoPE score (p=0.381). In PFO patients, higher scores on the RoPE score were associated with a higher likelihood of PFO being causal and a lower risk of stroke recurrence. Patients with lower scores on the RoPE score are more likely to have a stroke unrelated to their PFO and have been reported to be at higher risk of recurrence overall.[9,33] In our study, the presence of PFO in 44.8% (n=13) of individuals with a RoPE score ≥7 is consistent with this information.

The calculation of the RoPE score does not allow the inclusion of anatomical features of the PFO (e.g., atrial septal aneurysm, shunt size) that may affect the risk of recurrence and the benefits of closure.[9] In our study, while there was no significant relationship between the RoPE score and PFO closure, no statistically significant difference was found between the 90th-day mRS values according to the score (p>0.05). On average across studies, patients with ESUS are

younger and have lower initial stroke severity, lower cardiovascular risk factor burden, and lower mortality than patients with cardioembolic etiology.[18–21] The absence of death in our cases and the low NIHSS score are compatible with this information.

This study was designed to determine the underlying etiologies and their relationship with the RoPE score in young CS patients. It has been reported that a high score may be associated with carotid artery webs, apart from the possibility of symptomatic PFO.[34] In our study, no other cause that could be related to the RoPE score was found.

Conclusion

It is necessary to prevent stroke recurrences in young adults to increase life expectancy and minimize morbidity. In our study, PFO was the most common etiology in young CS and related to the RoPE score. Since determining the cause of stroke and treating etiology is essential, there is still a need for detailed research and new perspectives on etiology in patients with cryptogenic stroke.

Disclosures

Ethics Committee Approval: The Ethics Committee's approval of the study was received by the Health Sciences University Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee on 13.07.2023, with application file no. 2023/84 FSMEAH-KAEK. The study was conducted in accordance with the Declaration of Helsinki.

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