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Epidemiology, aetiology and clinical characteristics of ischaemic stroke in young adults: a retrospective study from Denizli, Türkiye

Genç erişkinlerde iskemik inmenin epidemiyoloji, etiyoloji ve klinik özellikleri: Denizli ili retrospektif tek merkez verileri

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Abstract

Purpose: The incidence of cerebrovascular disease (CVD) in young adults is approximately 6-26 per 100,000 worldwide, and this numbers are increasing every year. Stroke aetiology among young adults are more diverse than those among older adults and require extensive diagnostic work-up. The aim of our study is to determine risk factors and stroke etiology in stroke patients aged 45 years and younger, followed in our clinic for the last 10 years, and to compare them with literature.

Materials and methods: The study is included in the patients between the age of 18-45 years and are followed by Ischemic CVD in Pamukkale University Neurology clinic between January 2010 and November 2020.The clinical and demographic data of the patients were retrospectively analyzed.

Results: The most common risk factor was smoking (31.4%); hypertension (20.2%), diabetes mellitus (14.4%), hyperlipidemia (14.4%) and coronary arterial disease (11.6%) were following it. According to Trial of Org in Acute Stroke Treatment (TOAST)classification there were, large vessel disease in 13.4%, small vascular disease in 19.8%, cardioembolism in 16.7%, other determined aetiology in 11.5% and the most frequently stroke of undetermined etiology in 38.6%. The most common reason in other determined aetiology was Antiphospholipid Antibody Syndrome.

Conclusion: The incidence of young stroke is increasing every year and it is necessary to determine the underlying reasons to prevent and to give treatment for aetiology. Thus this will contribute to head off major health care costs, loss of workforce and to save young lives.

Key words: Young stroke aetiology, stroke in young adults, ischemic stroke.

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Öz

Amaç: Genç erişkinlerde serebrovasküler hastalık (SVH) insidansı dünyada yaklaşık 100.000'de 6-26'dır ve bu oran her yıl artmaktadır. Genç erişkinlerde inme etiyolojisi, yaşlılara göre daha çeşitlidir ve kapsamlı tanısal çalışma gerektirir. Çalışmamızın amacı, kliniğimizde son 10 yıldır takip edilen 45 yaş ve altı inme hastalarında risk faktörlerini ve inme etiyolojisini belirlemek ve literatürle karşılaştırmaktır.

Gereç ve yöntem: Çalışmaya Pamukkale Üniversitesi Nöroloji Kliniği'nde Ocak 2010-Kasım 2020 tarihleri arasında İskemik SVH ile takip edilen 18-45 yaş arası hastalar dahil edilmiştir. Hastaların klinik ve demografik verileri retrospektif olarak incelenmiştir.

Bulgular: En sık görülen risk faktörü sigara (%31,4) iken; hipertansiyon (%20,2), diabetesmellitus (%14,4), hiperlipidemi (%14,4) ve koroner arter hastalığı (%11,6) bunu izlemekteydi. Trial of Org in AcuteStrokeTreatment (TOAST) sınıflamasına göre etiyoloji: %13,4 büyük damar hastalığı, %19,8 küçük damar hastalığı, %16,7 kardiyoembolizm, %11,5 diğer etiyoloji idi ve hastaların çoğunu (%38,6) etiyolojisi belirlenemeyen inmeler oluşturuyordu. Belirlenen diğer etiyolojide en sık neden Antifosfolipid Antikor Sendromu idi.

Sonuç: Genç erişkinlerde inme insidansı her yıl artmakta olup, altta yatan nedenlerin belirlenmesi ve etiyolojisine yönelik tedavi verilmesi gerekmektedir. Böylece, bakım maliyetlerinin, işgücü kaybının önüne geçilmesine ve genç hayatların kurtarılmasına katkıda bulunulacaktır.

Anahtar kelimeler: Genç inme etiyolojisi, genç erişkinlerde inme, iskemik inme.

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Introduction

Stroke in young adults has a significant socioeconomic impact due to high health care costs and loss of workforce, and its incidence is increasing every year [1]. Although there is no official definition of the concept of young stroke, it generally included the ages of 18 to 50 [2]. In different studies, the lower limit was between the ages of 15-18, while the upper limit was taken as 45-55 years [2, 3]. The incidence of cerebrovascular disease (CVD) in young adults has been reported to be approximately 6-26 per 100.000 worldwide [4]. While this rate is 7-8 per 100.000 in Europe, it rises to 100 per 100.000 in Africa [1, 4]. "Young stroke" is more common in women under the age of 35, while it is more common in men between the ages of 35-50. It can be thought that the intensification of gender-specific risk factors such as pregnancy, postpartum period and oral contraceptive use in young women who are in reproductive age and the intensification of vascular risk factors in middle-aged men may lead to this difference in incidence [5, 6]. While unidentified rare causes constitute the majority of stroke causes in young adults, the incidence of large vessel atherosclerosis and small vessel disease increases with age [6]. Although the chance of surviving a stroke is higher in younger patients than in older age, survivors face complications such as recurrent paralysis, neuropsychiatric problems and seizures for a much longer period of time. Therefore, the causes of stroke among young adults are more diverse than those among older adults and require extensive diagnostic work-up [7].

The aim of our study is to determine risk factors and stroke etiology in stroke patients aged 45 years and younger, followed in our clinic for the last 10 years, and to compare them with literature data.

Material and method

The study was approved by the Clinical Research Ethics Committee of Pamukkale University.

In this study, records of 1189 patients who were between the ages of 18-45 and those hospitalized in our clinic with the diagnosis of ischemic CVD between January 2010 and November 2020 were retrospectively analyzed. Intracranial hemorrhage and venous sinus thrombosis were excluded. Demographic characteristics of the patients and risk factors that may cause stroke (hypertension, diabetes, hypercholesterolemia, smoking, hyperhomocysteinemia) were examined. Patients who were previously diagnosed with diabetes, were using antidiabetic drugs at the time of admission, or had a blood glucose level of ≥200 milligram/deciliter (mg/dL) at any time were considered as diabetic. A serum total cholesterol level ≥200 mg/dL was defined as hypercholesterolemia. Smoking cigarette 1 or more per day was evaluated as risk factors [7].

Blood tests to determine the etiology of stroke, hypercoagulability and vasculitis markers (Antithrombin III, protein C, protein S, activated protein C resistance, antinuclear antibody (ANA) profile, antiphospholipid antibodies, homocysteine, peripheral blood smear, serum lactate-pyruvate level, Anti-HIV, VDRL, toxoplasma, brucella antibodies, borrelia burgdorferi IgM-IgG.) Imaging methods (Carotid-vertebral Doppler ultrasonography (CVDUSG), aortic arch, carotid-vertebral CT (Computarized Tomography) angiography, cranial MRI (Magnetic Resonance Imaging), MR or CT angiography, Digital Subtraction Angiography (DSA) for patients deemed necessary) were examined. In addition, electrocardiogram, transthoracic echocardiography and/or transesophageal echocardiography examinations performed on the patients were evaluated.

Patients were divided into CVD subgroups according to the Trial of Org in Acute Stroke Treatment (TOAST) criteria. According to this classification, the following subgroups were determined:

1) Large vessel atherosclerosis

2) Cardiac embolism

3) Small vessel disease (Lacunar infarct)

4) Other determinedaetiology: Hematologic causes, coagulopathies, thrombocytosis, polycythemia, deficiency of coagulation inhibitors, antiphospholipid antibody syndrome, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) and other causes of CVD not listed above

5) Stroke of undeterminedaetiology [8, 9].

Statistics

Data analysis was performed with SPSS 24.0 package program. Mann Whitney U test was used to compare independent group differences. The relationships between continuous variables were analyzed with Spearman or Pearson correlation analyzes. The differences between categorical variables were analyzed with Chi-square analysis and *p* value below 0.05 was considered statistically significant

Results

A total of 1189 patients were examined and 148 (53%) of 277 patients included in the study were male and 129 (47%) were female. The mean age of the patients was 37.8±7.02 (20-45). Recurrent stroke was observed in 14 (5.1%) patients, and first stroke in 263 (94.9%) patients. Eighty-seven (31.4%) of the patients were smokers. Of 277 patients, 56 (20.2%) had hypertension, 40 (14.4%) had diabetes, 40 (14.4%) had hyperlipidemia, 32 (11.6%) had coronary artery disease. High homocysteine level in 113 patients, normal homocysteine level in 141 patients and low homocysteine level in 8 patients were determined, while homocysteine levels of 15 patients were not studied. According to the TOAST classification large vessel disease in 37 (13.4%), small vessel disease in 55 (19.8%), cardioembolism in 46 (16.7%), stroke due to other determined causes in 32 (11%, 5) and stroke of undetermined causes in 107 (38.6%) were detected among 277 patients (Table 1, 2).

Table 1. Risk factors of stroke in young adults

Risk factors	Number of patients	Percent
Smoke	87	31.4%
Hypertension	56	20.2%
Diabetis mellitus	40	14.4%
Hyperlipidemia	40	14.4%
Coronary artery disease	32	11.6%

Table 2. The subgroups of patients according to TOAST classification

TOAST Classification	Number of patients	Percent
Large vessel disease	37	13.4%
Small vessel disease	55	19.8%
Cardioembolism	46	16.7%
Other causes	32	11.5%
Cause unknown	107	38.6%
Total	277	100%

In the TEE imaging of the patients, PFO was detected in 17 patients (it was associated with ECO pathology in 9 patients). Holter ECG imaging was not performed in 17 (6.1%) of 277 patients, and Atrial Fibrillation was detected in only 7 (2.5%) of the remaining group. Holter ECG imaging of 253 patients was normal (91%).

Carotid vertebral Doppler ultrasonography was performed in 16 of the patients with large vessel disease, and total occlusion in the right Internal Carotid Artery (ICA) was detected in only one. A total of 227 patients underwent MR Angio/Arcus-carotid vertebral-brain CT angio, and thrombus in the vertebral artery in 6 patients, dissection of the vertebral artery in 1 patient, thrombus in the basilar artery in 2 patients, stenosis in the Posterior Inferior Cerebellar Artery (PICA) in 2 patients, dissection in the right ICA in 1 patient, aneurysm in the ICA in 2 patients, total occlusion in the ICA in 8 patients, 50% stenosis in the right ICA in 2 patients, stenosis of 30-60% in the left ICA in 4 patients, stenosis between 70-90% in 4 patients, occlusion in the M2 segment of the Middle Cerebral Artery (MCA) in 2 patients (one on the right , one on the left), vasculitic in 1 patient, 50% stenosis in the celiac artery in 1

patient, and aortic aneurysm in 1 patient were detected. DSA was performed on 34 patients and 22 were found to be normal. Vasculitis findings in 2 patients, ICA dissection in 1 patient, fibromuscular dysplasia in 1 patient, total occlusion in left ICA in 1 patient, 90% stenosis in ICA in 2 patients, thrombus in left MCA M1 in 2 patients, total occlusion in left MCA in 1 patient, thrombus in left ICA distal and MCA M1 in 1 patient were detected.

Considering other determined causes, AFAS in 3 patients, SLE in 6 patients, CADASIL in 3 patients, malignancy in 6 patients, polycythemia vera in 6 patients, Behçet's disease in 2 patients, sjögren's disease in 1 patient, scleroderma in 1 patient, Marfan syndrome in 2 patients, and ARA in 2 patients were detected. In the thrombophilia panel, homozygous MTHFR in 9 patients, homozygous factor V leiden in 3 patients, heterozygous factor V leiden in 3 patients, MTHFR heterozygous in 18 patients, PAI 4G/5G homozygous in 6 patients, PAI 4G/5G heterozygous mutations in 2 patients were detected.

Two hundred thirty-five (84%) of the patients were not using antiaggregant/anticoagulant drugs at the first admission. After treatment adjustment, it was determined that 133 of the patients used acetylsalicylic acid (asa), 57 of them clopidogrel, 24 of them dual asa+clopidogrel, 33 of them warfarin, 23 of them low-molecular-weight-heparin (LMWH),2 of them asa+warfarin, 3 of them Non-vitamin K antagonist Oral Anticoagulant (NOAK), 2 of them asa+dipyridamole.

Discussion

Stroke is a leading cause of death and adult disability worldwide. Early recognition and prompt treatment of stroke is essential to prevent or minimize morbidity and mortality. Every year, approximately 2 million young people worldwide suffer from stroke, which causes serious harm and financial burden to patients and their families [1, 10]. While the incidence of stroke in the elderly decreases from year to year, the incidence of stroke in the young people shows an increasing trend [1, 11, 12].

In the study of Ischemic Stroke in Young Adults aged 18-44 years in Northern Sweden, the incidence of stroke was found to be 11.3 per 100.000, and it was around 5 to 15 /100.000 per year in many European studies [7]. In our study, young age ischemic cerebrovascular disease was detected at a rate of 24% among all CVDs. In addition, the incidence of ischemic stroke is 53% higher in the male population, which is consistent with the literature.

The etiology and risk factors of young patients with ischemic stroke are in a wide and complex spectrum, such as migraine with aura, hereditary thrombophilia, hyperhomocysteinemia, cardiovascular risk factors and malignancy [5]. The prevalence of standard modifiable vascular risk factors in young stroke patients is different from that in older patients. Although modifiable risk factors are the same for both young and advanced age groups, the prevalence of these risk factors is not the same in these two age groups [13, 14]. In a study that collected data from hospital records of fifteen European cities, in young strokes, rare causes were found in 22%, cardioembolic causes in 17.3% (8.6% high-risk, 8.6% low-risk), small vessel disease in 12%, large vessel disease in 9% etiologically and the cause could not be determined in 40% of the patients. Among the known etiologies, the most common single cause was found to be cervical artery dissection [3, 4]. In our study, however, cervical artery dissection was never detected. The most common causes detected among other causes were Malignancy, SLE and polycytemia vera. Antiphospholipid Antibody Syndrome (APS) was also a common cause among the known other etiologies if it is taken into account that the most of the lupus patients have secondary APS due to Antiphospholipid Antibodies. Stroke, the cause of which cannot be determined according to TOASTcriteria, is the most common type in young patients [15]. Large vessel disease is observed less frequently in young stroke patients than in the elderly, and it has been replaced by other causes in the TOAST scoring [16]. In our study, large vessel disease in 37 (13.4%), small vessel disease in 55 (19.8%), cardioembolism in 46 (16.7%), stroke due to other causes in 32 (11.5%) and stroke of which the cause could not be found in 107 (38.6%) was detected. The most common cause is the group whose cause is unknown, which is compatible with the literature. The second cause was detected as small vessel disease, followed by cardioembolic causes. The reason for cardioembolic stroke is less frequent in this study may be the ethnicity and the

population has more vascular risk factors. Even the most of the classifications based on Europian population some specific ethnicities such as Asian population has adverse vascular risk factors in younger age. That can be explain the greater distribution of small and large vessel disease as ischemic stroke etiology in young patients. Although large vessel disease is the least common group in line with the literature, it was detected at a higher rate compared to the literature. Patients with stroke due to cardioembolism or large vessel atherosclerosis have the highest risk of recurrent stroke compared to other TOAST stroke subtypes, and secondary prevention is very important in these patients [17, 18]. Hereditary thrombophilias are one of the important risk factors. In a study performed by Mialovytska et al. [19] which included young ischemic stroke patients, it was found that increase was detected in the development of ischemic brain lesions with MTHFR gene mutation positivity, and there was a correlation between MTHFR gene mutation and high homocysteine. Also in our study, a gene mutation affecting the treatment regulation was found in 3.2% of the patients, in 9 patients, 5 of whom were homozygous for MTHFR and 3 of them were homozygous for factor V leiden. In the obtained data, high homocysteine level in 113 patients, normal homocysteine level in 141 patients and low homocysteine level in 8 patients were determined. The understanding that a high level of homocysteine in plasma may predispose to arterial or venous thromboembolism emerged more than 40 years ago when it was determined that patients with homocysteinuria are at high risk of early vascular disease. A meta-analysis by Holmen et al. [20] also points out the relationship between homocysteine levels and ischemic stroke risk. It was found that risk estimates reported in studies were significantly higher when homocysteine levels above 15 μmol/L were reached, indicating a possible nonlinear relationship between homocysteine and ischemic stroke. It is known that vasculitic processes are risk factors in young strokes, and many rheumatological diseases such as Behçet's, Sjögren's and SLE may cause stroke. In a cohort study performed by Hanly et al. [21], it was observed that neuropsychiatric findings in patients with SLE can often manifest themselves with stroke and TIAs. Hypercoagulability conditions caused by antiphospholipid hyperhomocysteinemia, high factor VIII, protein C deficiency and mutations such as methylenetetrahydrofolate reductase C677T, prothrombin G20210A and factor V Leiden (FVL) mutations are considered among possible causes despite different opinions. FVL is the most common hereditary coagulation disorder in many parts of the world. The role of this mutation in ischemic stroke patients is controversial. It demonstrated the function of FVL as an independent etiologic factor, especially in younger patients. On the other hand, there are many studies suggesting that FVL is a predisposing factor for ischemic stroke only when accompanied. Therefore, screening for coagulopathy is generally recommended in young stroke patients, especially in those whose disease origin is unknown [22]. In our study, polycythemia vera patients were found to be common among other causes, and the relationship between thrombosis and JAK 2 mutation is known even if there are no distinct myeloproliferative neoplasms in myeproliferative diseases. In addition, it should be kept in mind to consider screening for JAK 2 mutations in a young patient with cryptogenic stroke with or without polycythemia or thrombocytosis [23]. Although craniofacial dysplasia is rare, it is among the risk factors. Craniofacial fibrous dysplasia can cause various cerebrovascular diseases by causing narrowing of intracranial vessels and alteration of general hemodynamics of intracranial vessels. A possible mechanism considered here is that it causes neurovascular compression, resulting in hemodynamic changes and decreased cerebral perfusion [24]. Regarding cardiovascular risk factors, Sub-stenotic atherosclerosis, left atrial dysfunction, and occult atrial fibrillation are probably the most common causes, but undetected malignancy, hypercoagulable states, and PFO-related stroke are alternative causes to be considered. Many studies performed with patent foramen ovale (PFO) have been shown to be associated with stroke. It suggests a potential etiological link, by increasing over 40% in the Cryptogenic stroke population; however, specific clinical and cardiac structural variants that conclusively indicate causation are not yet known [25]. The most relevant complication of AF is cardioembolic stroke. Thrombus often form in the left atrial appendage (LAA) due to abnormal blood flow in the left atrium associated with erratic electrical signals and lack of coordinated atrial contractions, in addition to

endothelial dysfunction and other prothrombotic conditions. Once 'released' this thrombus could embolize into peripheral or (more commonly) cerebral artery beds. In particular, patients with AF-related embolic stroke are thought to have worse outcomes than those with non-AF-related strokes [26, 27]. Both North American and European guidelines support the use of the CHA2 DS2 -VASc score to classify patients with AF according to the risks of stroke and systemic thromboembolism. This scoring is very important in determining the risk of AF [28, 29]. Other causes include IS arterial dissection in Young adults, Moyamoya disease (MMD), primary and secondary central nervous system vasculitis, antiphospholipid syndrome (APS), reversible cerebral vasoconstriction syndrome (RCVS), cerebral vein thrombosis (CVT), and genetic diseases. Cerebral autosomal dominant arteriopathies with subcortical infarcts and leukoencephalopathy (CADASIL) and Fabry disease should be kept in mind [30]. Considering the treatment arrangement in a study performed by Kunt et al. [31], examining the clinical and demographic characteristics of patients with stroke, the relationship between medicine use and cerebrovascular events was investigated. It was observed that stroke occurred in 527 patients (46.3%) while using antiaggregant or anticoagulant, and when the medicines used were examined, it was found that there was no significant difference between the patient groups in terms of the use of acetylsalicylic acid, clopidogrel and warfarin.

In summary, the incidence of stroke in young people is increasing every year, and it is very important to determine the underlying etiology and to give treatment for the exact reason. The causes of stroke among young adults are more diverse than those among older adults and require extensive diagnostic work-up. Although the chance of surviving a stroke is higher in younger patients than in older age, survivors face complications such as recurrent paralysis, neuropsychiatric problems and seizures for a much longer period of time. Therefore, preventing stroke in young adults will contribute to head off major health care costs, loss of workforce and to save young lives.

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Authors' contributions to the article

S.B.A.: study design, data collecting, data analysis.

Z.Ü.: data analysis, writing.

Ç.H.Ö.: data analysis, writing, supervisor.