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ARAŞTIRMA / RESEARCH

Relationship between thrombophilia status and short-term outcome in young adults with ischemic stroke

Genç inmeli hastalarda trombofili durumunun kısa dönem sonlanım ile ilişkisi

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Abstract

Purpose: Ischemic stroke is a serious health condition in patients with young adults. This study aims to determine thrombophilia polymorphisms in young patients with ischemic stroke and associations with other risk factors.

Materials and Methods: We evaluated 64 patients with ischemic stroke under 50 years old. Computerized Tomography Angiography, Holter Electrocardiography, Transthoracic Echocardiography, thrombophilia status, and Modifying Rankin Scale (MRS) in baseline and first month findings were recorded. We analysed the association between thrombophilia status and short-term outcome in young adults with ischemic stroke.

Results: 64 patients (38 male, 59.4%) were included in our study. The mean age of the patients were 42.48±6.73. The thrombophilia status showed that the most frequent polymorphism was MTHFRA1298T mutation (18.8% homozygous, 43.7% heterozygous). The second was MTHFRC677T and the third polymorphism was Factor 5 Leiden mutation, of 21.8% was homozygous and 34.4% was heterozygous mutation. 7.8% of the patients have atrial fibrillation, 17.2% of them have patent foramen ovale, and 7.8% have elevated pulmonary artery pressure (>30 mmHg). Thrombophilia status and PFO were not associated with IS in young adults.

Conclusion: Young patients with ischemic stroke have several thrombophilial polymorphism; however, we did not detect any association with IS. Young patients with ischemic stroke have also many classic risk factors which should be treated appropriately. Patent foramen ovale is another remarkable pathology and more researches are needed to realize its relation with ischemic stroke in young adults.

Keywords:. Ischemic stroke, thrombophilia, atrial fibrillation, patent foramen ovale

Öz

Amaç: İskemik inme genç kişilerde ciddi sağlık sorunlarına yol açan bir durumdur. Bu çalışmada da genç iskemik inmeli hastalarda trombofili polimorfizmlerinin iskemik inme ve diğer risk faktörleri ile ilişkisi incelenmiştir.

Gereç ve Yöntem: Çalışmaya 50 yaş altında toplam 64 adet iskemik inme geçiren hasta dahil edildi. Hastaların Bilgisayarlı Tomografi Anjiografi, Holter Elektrokardiografi, Transtorasik Ekokardiyografi, trombofili durumları ile baseline ve 1. ay Modifiye Rankin Skalaları kayıt altına alındı. Hastaların trombofili durumları ile kısa dönem iyilik hali arasındaki ilişki değerlendirilmiştir.

Bulgular: Çalışmamıza 64 hasta (38 erkek, % 59.4) dahil edildi. Hastaların ortalama yaşı 42,48 ± 6,73 idi. En sık görülen polimorfizm MTHFRA1298T mutasyonu (% 18.8 homozigot, % 43.7 heterozigot) idi. İkinci sıklıkta MTHFRC677T mutasyonu ve üçüncü olarak da Faktör 5 Leiden mutasyonu (% 21.8 homozigot ve % 34.4 heterozigot) gözlendi. Hastaların % 7,8'inde atriyal fibrilasyon, % 17,2'sinde patent foramen ovale ve % 7,8'inde artmış pulmoner arter basıncı (> 30 mmHg) izlendi. Genç yetişkinlerde trombofili varlığı ve PFO'nun iskemik inme ile ilişkisi saptanmadı.

Sonuç: Genç inmeli hastalarda birçok trombofili polimorfizmi mevcuttur ancak iskemik inme ile ilişkisi saptanmamıştır. Bu hastalarda iskemik inme ile ilişkili birçok klasik risk faktörü tespit edilmiş olup uygun şekilde tedavi edilmelidir. Diğer önemli bir faktör de patent foramen ovale varlığı olup iskemik inme ile ilişkisinin değerlendirilmesi için daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler: İskemik inme, trombofili polimorfizm, atriyal fibrilasyon, patent foramen ovale

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INTRODUCTION

Ischemic stroke (IS) is the fifth cause of mortality in the United States of America (USA), and it is still a leading cause of morbidity[1]. The incidence of IS varies among different countries and regions. It is 247 per 100000 person-years in China[2]. The annual number of patients with stroke is almost 800000, including the first and recurrent strokes in the USA[3]. The incidence increases with age; however, IS occurs in young adults, children, and even infants[4,5]. The overall incidence of IS in young adults has a wide range varying from 3 to 23/100000 patients[6].

Older patients have classic risk factors including hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HPL), coronary heart disease (CHA), and smoking for IS; however, patients with younger age have additional risk factors like vasculopathy, cardiac structural disorders, hematologic abnormalities, drug abuse, and dissections[7]. Drug use has been increasing in recent years, and it is becoming a conspicuous risk factor in young patients for stroke. These risk factors for IS among young adults come from several studies and population-based cohorts. The biggest cohort involving 1008 patients from Finland showed that the leading risk factors were HPL (60%), HT (44%), and smoking (39%). The most common etiologic disorders were cardioembolism (20%) and cervical arterial dissection (15%)[8].

The mortality and morbidity are decreasing with new approaches; however, IS is increasing in patients under 50 years old. It is important to note that these patients are in their most productive age and morbidity in young patients has essential consequences, including social, familial, and economic burdens[9]. Therefore, identifying risk factors in patients with IS has a crucial role in preventing first stroke and recurrences.

Inherited or acquired thrombophilias are associated with an increased risk of venous thrombosis[10]. The role of thrombophilias in arterial stroke remains controversial. De Stefano et al. reported a study including 72 young adults under 50 years old with IS. They found a 3.8-fold increased risk for IS with heterozygot factor II G20210A mutation[11]. In a past meta-analysis including 18 case-control study, Hamedani et al. found that factor V Leiden mutation was associated with IS in young patients[12]. In another study, methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C polymorphisms were found to be related with IS in young adults[13]. Several studies detected a significant association; however, others found no relationship between arterial strokes and thrombophilia status[14,15,16]. Therefore, the primary aim of this study is to determine the effect of thrombophilia status over the morbidity outcomes of young IS patients. The second aim is to establish the association between well-known risk factors and morbidity in these patients.

MATERIALS AND METHODS

This is a retrospective and cross-sectional study which were conducted between January 2019 and July 2020 in young patients with IS. The study was performed in İzmir Katip Çelebi University Atatürk Training and Research Hospital, Department of Neurology. This study was approved by the İzmir Katip Çelebi University Faculty of Medicine Ethics Committee (Decision Date: 22.10.2020, 1005 Approval Number). It was conducted in accordance with the Helsinki Declaration, and all the participants provided informed consent.

Sample

Patients with IS under 50 years old were classified as young adults and we included patients aged between 18 to 50 years old in our study. We analysed data of 298 patients who were hospitalized during January 2019 and July 2020 and we excluded 234 patients due to age criteria. In addition, patients who do not have signs of ischemia in magnetic resonance imaging (MRI) were excluded. Patients were followed-up at least one month after IS to determine disability status.

Procedure

There are many different etiological reasons for ischemia in young patients with IS. Therefore, many different examinations involving routine biochemical blood tests, autoimmune antibody status, diffusion MRI, Computerized Tomography Angiography (CTA), Holter Electrocardiography (H-ECG), Transthoracic Echocardiography (T-ECHO) findings, and thrombophilia status are performed routinely in young patients during their hospitalization in our Neurology Department. Genomic DNA to examine thrombophilia status was obtained from peripheral blood leukocytes with a DNA extraction kit (QIAmp blood kit; Qiagen GmbH, Hilden, Germany). A multiplex amplification with biotinylated primers was used to amplify the

genomic DNA. The polymerase chain reaction products are then reverse hybridized using the GenoType test based on DNA.STRIP technology. The results were determined according to the presence of heterozygous and homozygous mutations.

Sixty-four slice brain CT were applied to exlude hemorrhage and CTA were applied to determine the stenotic vascular structure. Diffusion MRI was taken to confirm ischemia. All patients underwent H-ECG and T-ECHO to determine rhythm disturbances, presence of any structural heart pathology including patent foramen ovale, and the presence of thrombus.

The blood samples for thrombophilia status were evaluated in Department of Medical Genetics and it includes antithrombin III, protein C, protein S levels, MTHFR C677T and 1298T, prothrombin, factor 5 Leiden, PAI 14G/15G, ß-fibrinogen, factor XIIIV34L, and GPIIIAL33P polymorphisms.

We recorded demographic data, involvement of vascular territory, and co-morbid diseases. Patients were diagnosed as hypertension with blood pressure above 130 mmHg systolic and 80 mmHg diastolic in serial measurements. LDL> 70 mg/dL was hyperlipidemia. The diagnosis of DM was made according to random glucose test: ≥ 200 mg per dL with symptoms or HbA1c measurement ≥ 6.5 percent.

Coronary artery disease was diagnosed according to the findings of coronary angiography applied by a cardiologist. Modified Rankin Scale (MRS) were also analyzed to determine the disability status of the patients at baseline and first month. We applied H-ECG and T-ECHO to all patients and assessed the cardiac pathologies related to IS. Finally, we evaluated the relationship between thrombophilia status and short-term disability status of the patients.

Statistical analysis

Statistical analysis of the data was performed using SPSS 22.0 (IBM Corporation, Armonk, NY, USA) package program. In data analysis, the distribution of continuous variables was determined with the Shapiro-Wilk normality test. Descriptive statistics were shown as mean and standard deviation or minimum-maximum for continuous variables, and as the case number and (%) for categorical variables. The relationship between qualitative variables was examined using the Pearson Chi-square test. Values of $p < 0.05$ for all tests were considered statistically significant.

RESULTS

We included 64 patients with IS of which 38 (59.4%) were males. The mean age of the patients were 42.48±6.73 (21-49). Approximately one in four of the patients had a family history of young stroke. The most common risk factor was HPL (64.1%). Smoking (53.1%) and HT (37.5%) were the following risk factors for IS. As expected, the most common vascular territory was middle cerebral artery (MCA) (51%). Posterior cerebral artery (PCA) (19%) and vertebrobasiler artery (VBA) (16%) involvement were the following vascular territories. All of our patients underwent to a CTA assessment and we recorded >70% as serious stenosis. 10.9% of the patients had Internal Carotid Artery (ICA) stenosis, 7.8% of them had MCA stenosis, and 7.8% of them had VBA stenosis (Table 1).

Table 1. Demographical and clinical characteristics of patients

Demographics	**Patients (n=64)**
Age, mean±SD (range)	42.48±6.73 (21-49)
Female /Male n (%)	26 (40.6%) /38 (59.4%)
Family history of young stroke	17 (26.6%)
Co-morbidity	
Hypertension	24 (37.5%)
Diabetes Mellitus	11 (17.2%)
Smoking	34 (53.1%)
Coronary Artery Disease	6 (9.4%)
Hyperlipidemia	41 (64.1%)
Vascular territory	
Anterior Cerebral Artery	4 (6%)
Middle Cerebral Artery	33 (51%)
Posterior Cerebral Artery	12 (19%)
Vertebrobasilar Artery	10 (16%)
Multiple vascular involvement	5 (8%)
Stenosis >70% in CT Angiography	
Internal Carotid Artery	7 (10.9%)
Middle Cerebral Artery	5 (7.8%)
Basilar Artery	2 (3.1%)
Vertebral Artery	3 (4.7%)
No significant stenosis	47 (73.4%)

SD: Standart deviation, CT: Computerized Tomography

The thrombophilia status showed that the most frequent polymorphism was MTHFRA1298T mutation (18.8% homozygous, 43.7% heterozygous).

The second was MTHFRC677T and the following polymorphism was Factor 5 Leiden mutation, of 21.8% was homozygous and 34.4% was heterozygous mutation (Table 2).

The assessment of cardiac examination showed that 7.8% of the patients have atrial fibrillation (AF), 17.2% of them have patent foramen ovale (PFO), and 7.8% have elevated pulmonary artery pressure (>30 mmHg). In addition, more than half of patients have mitral and tricuspid insufficiency (56.3%), as shown in Table 3. Patients with PFO did not show any relationship with any thrombophilia polymorphism. Baseline MRS revealed that only 1 patient (1.6%) had MRS 0 at the application; however, 34 patients (53.1%) have MRS 0 at 1st month assesment ($p<0.001$). MRS was ≤ 2 in 87.5% of the patients at baseline and it was 93.7% at 1st month ($p=0.02$) (Table 4).

The analysis between thrombophilia status, baseline MRS and 1st month MRS showed no relationship ($p>0.05$). Likewise, otoantibody status including antiphospholipid, anticardiolipin, anti Ro-La, Anti nuclear and anti ds-DNA antibody did not show any association with MRS ($p>0.05$).

Table 2. Thrombophilia status of the patients

	MTHFR C677T	**MTHFRA 1298T**	**Prothrombin**	**F5 Leiden**	**PAI-14G/15G**	**ß-fibrinogen**	**Factor XIIIV34L**	**GPIII AL33P**
Homozygous	12 (18.8%)	12 (18.8%)	10 (15.6%)	14 (21.8%)	9 (14%)	7 (10.9%)	4 (6.2%)	2 (3.1%)
Heterozygous	25 (39%)	28 (43.7%)	8 (12.6%)	22 (34.4%)	18 (28.1%)	15 (23.4)	10 (15.6%)	12 (18.8%)
No mutation	27 (42.2%)	24 (37.5%)	46 (71.8%)	28 (43.8%)	37 (57.9%)	42 (65.7%)	50 (78.1%)	50 (78.1%)

MTHFR: Methylene Tetrahydrofolate Reductase

Table 3. Cardiac findings of the patients

	n (%)
Atrial fibrillation	5 (7.8%)
Patent foramen ovale	11 (17.2%)
Aortic insufficiency	16 (25%)
Mitral insufficiency	36 (56.3%)
Pulmonary insufficiency	4 (6.3%)
Tricuspid insufficiency	36 (56.3%)
Aortic stenosis	1 (1.6%)
Tricuspid stenosis	1 (1.6%)
Pulmonary stenosis	1 (1.6%)
Elevated Pulmonary artery pressure (>30 mmHg)	5 (7.8%)

Table 4. Baseline and 1 st Month Modified Rankin Scale

Baseline		**1 st Month**	
MRS	n (%)	MRS	n (%)
0	1 (1.6%)	0	34 (53.1%)
1	42 (65.6%)	1	23 (35.9%)
2	13 (20.3%)	2	3 (4.7%)
3	4 (6.3%)	3	0 (0%)
4	3 (4.7%)	4	1 (1.6%)
5	1 (1.6%)	5	2 (3.1%)

MRS: Modified Rankin Scale

DISCUSSION

In this study, we did not detect any relationship between IS in young patients and thrombophilia status. In addition, patients with PFO did not have association with thrombophilia polymorphism. The other featured result of this study was the high prevalence of atherosclerotic risk factors in our patients. Heterozygote MTHFR and Factor 5 Leiden mutation were the most frequent inherited thrombophilia in our patients; however, these mutations were not associated with increased risk of IS in our young patients. Pahus et al. showed a relationship between thrombophilia polymorphism and transient ischemic attack/amorozis fugax. On the contrary, they did not showed an association between IS and thrombophilia status[10].

Generally, there is no clear evidence that hypercoagulable states lead to arterial ischemia. Even if hypercoagulability is detected, treatment change is often not recommended[17]. Many neurologist order these thrombophilia tests as a part of differential diagnosis in young adults. Even if many polymorphisms were detected, they are not generally clinically relevant. It is important to decide that the etiology of IS is related to atherosclerosis or IS occurred due to a hypercoagulable state. Attributing causality to an arterial pathology may lead to long-term anticoagulant treatment, which may cause hemorrhagic side effects[18]. The other recommendation for neurologist is to assess cardiac structures and vessel imaging before thrombophilia testing[19].

Omran et al. published a study including 196 young patients with IS. They analyzed the association of hyperhomocysteinemia, MTHFR or Factor V Leiden gene mutation heterozygosity, however, no significant relationship was found between the polymorphism and the presence of IS[20]. Pahus et al. investigated different types of ischemic cerebrovascular disease including transient ischemic attack, amorozis fugax and ischemic stroke. The study had 685 patients and they did not determine any significant association between IS and positive thrombophilia testing[21].

PFO is another controversial issue in patients with young stroke. The possible mechanism is paradoxal embolism leading to arterial stroke[22]. 25% of the general population have PFO; however, 50% of the patients with IS are expected to have PFO[23]. Florez et al reported a study with IS patients whether the thrombophilia status is associated with the presence of PFO[24]. The study involved 280 patients and they did not detect a relationship between thrombophilia and PFO. Inline with several studies, only 17.2% of our patients had PFO and we also did not detect any association with the presence of stroke, MRS and positive thrombophilia testing. PFO is still controversial in patients with IS and more studies are needed.

AF is one of the possible cause of cardioembolic stroke, especially in patients older than 50 years old[25]. The young patients with IS should be evaluated in terms of AF. In HISTORY study, authors reported AF, mostly paroxismal, in 10.2% of the 98 young patients with IS. They recommend long-term H-ECG monitorization to detect AF[26]. In our study, we showed that 7.8% of our patients have AF. Our rate was quite similar although we could monitor them for just 24 hours. We believe that higher rates could be detected with long-term H-ECG monitorization.

MRS showes disability status of patients with IS. Outcomes depend on different factors. Severity of stroke, previous cerebrovascular events and the presence of DM predicts 3 month outcome in a Swiss study[27]. In our study, we realized that 1st month outcome was related with the severity of IS and many of our patients showed a favorable outcome.

This study have several limitations. First, this study has a retrospective design. Second, we have small number of patients. Third, we did not evaluated long-term outcomes. Fourth, we could not assesed all patients with transesophageal ECHO. Fifth, our study did not have a control group including people without IS.

In conclusion, young patients with IS have several thrombophilial polymorphism; however, we did not detect any association with IS. Young patients with IS have also many classic risk factors which should be treated appropriately. PFO is another remarkable pathology and more researches are needed to realize its relation with IS in young adults.

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