ORIGINAL ARTICLE

ARAŞTIRMA YAZISI

INVESTIGATION OF RISK FACTORS IN CRYPTOGENIC ISCHEMIC STROKE

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ABSTRACT

INTRODUCTION: Cryptogenic ischemic stroke (CS) includes 30-40% of all ischemic strokes. Several studies using different methods of prolonged cardiac monitoring determined atrial fibrillation (AF) in 12-25% of CS patients, however these findings are not enough to explain the etiology of most of the CSs. Our aim is to research thromboembolic sources and vascular risk factors in CS patients.
METHODS: The study enrolled 125 patients older than 45 years, 65 of them with CS according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. Control group included patients admitted cardiology outpatient clinic with symptoms of nonspecific chest pain or dyspnea without cerebrovascular diseases. Patients with any history of AF or paroxysmal AF, intra-cardiac thrombus or valvular heart disease and left ventricular dysfunction, heart failure were excluded. Cardiovascular risk factors, left atrium diameter, left ventricle ejection fraction (EF) (%) and 24-hour Holter ECG monitoring were examined. Blood total cholesterol, LDL, HDL, urea, creatine levels were also analyzed and compared.
RESULTS: Hypertension, diabetes mellitus, coronary artery diseases were more prevalent in the study group (p<0.05). LDL, total cholesterol and blood urea levels were significantly higher and HDL was lower in the study group (p<0.05). There was no significant difference between two groups in terms of Holter ECG results. In the study group, six patients had non-sustained AF episodes (<30 sec.) and two had paroxysmal AF episodes. In control group only two patients had frequent AF episodes continuing >30 sec.
DISCUSSION and CONCLUSION: Cardiovascular risk factors leading thromboembolism were prominently higher in CS patients, long-term ECG monitoring may explain only the cardioembolic sources due to arrhythmia. Investigation of thromboembolic sources is vital for determining the etiology of CS.
Keywords: Cryptogenic stroke, holter ECG, cardiovascular risk factors, thromboembolism.

KRİPTOJENİK İSKEMİK İNMEDE RİSK FAKTÖRLERİNİN ARAŞTIRILMASI

ÖZET

GİRİŞ ve AMAÇ: Kriptojenik iskemik inme (Kİ) tüm iskemik inmelerin %30-40'ını kapsamaktadır. Farklı çalışmalarda değişik uzun süreli kardiak monitorizasyon metodları kullanılarak Kİ hastalarının %15-25'inde atrial fibrilasyon (AF) saptanmıştır, ancak bu bulgular Kİ etyolojisinin büyük bir kısmını açıklamada yeterli değildir. Amacımız Kİ hastalarında tromboembolik kaynakların ve vasküler risk faktörlerinin araştırılmasıdır.
YÖNTEM ve GEREÇLER: Çalışmaya toplam 125 hasta dahil edildi, bunların 65 tanesi Trial of Org 10172 in Acute Stroke Treatment (TOAST) kriterlerine göre seçilmiş Kİ hastalarıydı. Kontrol grubuna kardioloji polikliniğine non spesifik göğüs ağrısı veya nefes darlığı ile başvuran ve serebrovasküler hastalığı olmayanlar dahil edildi. AF veya paroksismal AF öyküsü olanlar, intrakardiak trombus, kalp kapak hastalığı ve sol ventrikül disfonksiyonu veya kalp yetmezliği olan hastalar çalışmadan dışlandı. Kardiovasküler risk faktörleri, sol atrium çapı, sol ventrikül ejeksiyon fraksiyonu (EF)(%) ve 24 saat holter EKG monitorizasyonu incelendi. Kan total kolesterol, LDL, HDL, üre, kreatin düzeyleri analiz edildi.
BULGULAR: Çalışma grubunda hipertansiyon, diyabet, koroner arter hastalığı anlamlı olarak yüksek saptandı (p<0.05). LDL, total kolesterol ve kan üre seviyeleri çalışma grubunda anlamlı yüksekti ve HDL seviyesi ise düşüktü (p<0.05). Holter EKG sonuçları açısından her iki grup arasında anlamlı fark saptanmadı. Çalışma grubunda, altı hastada sürekli olmayan AF epizodları (<30 sn.) ve iki hastada ise paroksismal AF epizodları vardı. Kontrol grubunda ise sadece iki hastada >30 sn. süren sık AF epizodları mevcuttu.

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TARTIŞMA ve SONUÇ: Kİ populasyonunda tromboembolizme yol açan kardiovasküler risk faktörleri belirgin yüksek saptandı, uzun sureli EKG monitorizasyonu sadece aritmiye bağlı kardioembolik kaynakların nedenini açıklayabilir. Tromboembolik kaynakların araştırılması Kİ etiyolojisinin saptanmasında önemli yer tutmaktadır.

Anahtar Sözcükler: Kriptojenik inme, holter EKG, kardiovasküler risk faktörleri, tromboembolizm.

INTRODUCTION

Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, which is the one most commonly used in clinical practice, cryptogenic ischemic stroke (CS) is defined as brain infarction that is not attributable to a source of definite cardio-embolism, large artery atherosclerosis, or small artery disease despite a standard vascular, cardiac, and serologic evaluation. It accounts for 30-40% of ischemic strokes in recent stroke registries and databases (1,2,3,3,4,5).

Occult atrial fibrillation (AF) is often suspected in cases of CS, and determination of AF occurrence is considerable critical, because it changes preventive therapy from antiplatelet agents to a more effective prophylaxis with oral anticoagulation (1,2,5,6). AF is a common cause of cardio-embolism, but it can be difficult to diagnose due to asymptomatic or paroxysmal episodes (7,8,9,10). There is not a consensus among experts regarding the duration of cardiac monitoring and insufficient data to support the optimal cost-effectivity (5,10,11,12).

In clinical practice external 24-hour ECG recording (Holter) is frequently used, entailing the detection of previously undetermined AF in approximately 2% of stroke patients. Besides extending the ECG recording time from 24 to 72 hours increases the prevalence of paroxysmal AF after stroke from 1.2% to 6.1% (2,8). Even in selected high-risk patient group, the use of 24-h ECGs only improves new AF detection rates to just 10%. According to the CHA2DS2-VASc score, the stroke linked to AF is related not only to the arrhythmia but also to several clinical characteristics and ranges from 1.3 to 15.2%. Applying the higher rate of stroke to CS population, the final rate of ischemic events related to AF episodes should be no more than 2.43% (1). The other possible mechanisms are aortic atheromatous disease, or other cardiac sources such as patent foramen ovale (PFO), atrial or ventricular septal defect (ASD, VSD), undefined thrombophilia, subcritical cervicocerebral arterial steno-occlusive disease and other vasculopathies (13).

In this study, we investigated and analyzed the vascular risk factors, thromboembolic sources and Holter ECG results between the control and CS patients. We also researched the etiological risk factors of CS according to TOAST criteria.

MATERIAL AND METHODS

Study subjects

This study enrolled 65 CS patients selected from 354 consecutive acute ischemic stroke patients with undetermined origin according to TOAST criteria between January 2015 and March 2016, retrospectively. Control group (n=60) was selected consecutively from the patients admitted to cardiology outpatient clinic with the symptoms of nonspecific chest pain and dyspnea and without any valve pathologies, heart failure, arrhythmia, coroner artery disease and cerebrovascular diseases.

All patients were older than 45 years. This study was approved by the local ethic committee of education and research hospital (19.01.2016/decision no: 13) and written consents were taken from all subjects.

TOAST criteria

CS is a diagnosis of exclusion based upon a through investigation for potential stroke etiologies. The diagnosis of CS is made when a standard evaluation reveals no probable cause; there is no definite evidence of cardio-embolism, large artery atherosclerosis, small artery disease, or other determined etiology, and no evidence of AF on a 12-lead electrocardiogram (ECG) (13).

For the diagnosis of CS; brain imaging (cranial and diffusion MRI), CT or MR angiography, transthoracic echocardiography (TTE) and 24 hour Holter ECG were performed. Via TTE left ventricle ejection fraction (LVEF) and left atrium diameter (LAD) of all patients were measured. Holter ECG results were reviewed by a cardiologist.

Patients younger than 45 years, carotid artery stenosis ≥ %50 demonstrated on BT or MR angiography, patients with any history of AF or paroxysmal AF, any other arrhythmia intra-cardiac

thrombus or any other cause of cardiac embolism, valvular heart disease and left ventricular dysfunction, heart failure were excluded. In addition patients with aortic pathology, mechanical heart valve PFO, ASD or VSD revealed on TTE and hypercoagulable states, patients with primarily hemorrhagic stroke, or acute large vessel dissection and lacunar strokes were not included in the study group.

The patients of study group were included meeting the TOAST criteria as mentioned. Control group was selected from patients admitted to cardiology outpatient clinic who were taken 24 hour Holter ECG with symptoms of dyspnea or nonspecific chest pain and without cerebrovascular diseases and cardiac pathology.

Hypertension (HT), diabetes mellitus (DM), coronary artery diseases (CAD), chronic renal failure (CRF), LAD, Holter ECG results and LVEF were compared between groups. Routinely studied blood laboratory results; LDL, HDL, total cholesterol, triglycerides, hemoglobin, platelets, urea, creatine were also analyzed and compared.

Holter ECG

Three-channel NORAV DL 800 Holter ECG device was used to record 24 hour ECG results of patients. All records in NORAV DATABASE were analyzed by two independent observers (Holter ECG nurse and a cardiologist) separately. Finally the results were also examined and analyzed in detail by another cardiologist. Atrial fibrillation, atrial or ventricular ectopic activity, arrhythmias, tachycardia and other cardiac rhythm pathologies were noted.

Laboratory tests

Following a 8-hour fasting period, 5-ml venous blood was drawn from ante-cubital fossa for complete blood count and routine biochemical blood tests (glucose, urea, creatine, HDL, LDL, triglycerides, total cholesterol, Ca++, K+, Cl-, liver enzymes, total and direct bilirubin, total protein, albumin) and also erythrocyte sedimentation rate (ESR), C-reactive protein were measured.

Statistical analyses

All data were analyzed using the Statistical Package for the Social Sciences, ver. 22.0, for Windows (SPSS; Chicago, IL). Numeric and categorical variables were compared with Chi-square and Student T-test between the groups. P-values < 0,05 were accepted to indicate statistical significance.

RESULTS

In the study group, 96.9% (n=63) of patients had mRS: 0-2 and only two (3.1%) of them had mRS: 3, further the mean value of NIHSS was 3,75±2,31. Nineteen patients had multiple infarct areas and 46 patients had single infarct area. Most of them were in hemispheric and thalamic localization (n=38), the second most was basal ganglia (n=13) and the third was pons localized (n=10). Only four of them had cerebellar infarct.

There was no difference between the groups in terms of age and gender. HT, DM, CAD were significantly prevalent in the study group (Table I).

Table I. Demographical parameters.

Parameters	Study group (n:65)	Control group (n:60)	P value
Age	60.5±11.4	57.2±13.6	0.150
Female (%)	38.4%	55%	0.064
HT (%)	63.1%	40%	**0.010**
DM (%)	41.5%	20%	**0.009**
CAD (%)	16.9%	0 %	**0.001**
CRF (%)	12.3%	6.6%	0.285

HT: hypertension, DM: diabetes mellitus, CAD: coronary artery diseases, CRF: chronic renal failure.

LDL, total cholesterol and blood urea levels were significantly higher in the study group. HDL was higher in the control group. There was no difference in terms of other parameters (table II).

Table II. Biochemical blood parameters.

Parameters	Study group (n:65)	Control group (n:60)	P value
Hemoglobin	13.4±1.8	13.2±1.1	0.373
LDL	150.6±59.7	118.3±33.8	**0.001**
HDL	42.1±10.3	48.7±11.1	**0.001**
Total cholesterol	222.8±53	197.5±45.6	**0.005**
Triglycerides	192.0±142.4	166.6±84.6	0.223
Platelet	260.6±91.9	271.2±116.4	0.576
Urea	43.3±20.6	32.3±12	**0.001**
Creatine	1.39±1.9	1.00±0.7	0.122

LDL: low-density lipoprotein HDL: high-density lipoprotein.

There was no difference between the results of Holter ECG and LAD. Additionally mean LVEF was significantly higher in the control group, but in normal ranges (Table III).

In the study group, six patients had non-sustained AF episodes (<30 sec.) and two had paroxysmal AF episodes. In control group only two patients had frequent AF episodes continuing >30 sec.

Table III. Cardiac parameters.

Parameters	Study group (n:65)	Control group (n:60)	P value
AF episodes	2=sustained 6=non sustained	2=sustained 0=non sustained	
AEA, VEA tachycardia	40	41	0.181
NSR	17	17	
Left atrium diameter	36.04±5.64	34.56±5.23	0.131
Left ventricle EF (%)	59.26±2.89	60.26±2.59	**0.043**

AEA: Atrial ectopic activity VEA: Ventricular ectopic activity NSR: normal sinus rhythm EF: ejection fraction AF: atrial fibrillation.

DISCUSSION

Most of the etiological factors of CS are unknown. In clinical practice Holter monitoring (HM) is frequently used to clarify these unknown factors, but external HM for 24 to 72 hours detected AF only in the range of 2,4% - 6,0% (11). Both the CRYSTAL AF and EMBRACE randomized multi-center large trials demonstrated the incremental diagnostic value of extended cardiac monitoring over contemporary practice (1). Obviously ideal timing and duration of monitoring techniques are unclear currently in clinical guidelines. The duration can be extended to 7-30 days as mentioned in literature (8,14). A meta-analysis of 32 studies by Kishore et al found a diagnosis of AF in 11.5% in this population. Unfortunately, differences in enrollment criteria, follow-up duration, and end point definition make comparison between any of these studies difficult (11,15).

Long duration of HM should be applied to the patients with elevated cardiac troponin I (cTnI) levels and multiple infarcts as demonstrated in literature (6,16). Boire et al found that AF was more prevalent in patients with elevated cTnI levels than patients with normal cTnI levels using ECG and 24-hour HM (6). Additionally, it was asserted that multiple acute and chronic cerebral infarcts on CT and MRI were associated with paroxysmal AF (PAF) (16). However long-term ECG monitoring could not explain the diagnosis in approximately 90% of patients with CS. The importance of understanding these aspects resides in the fact that diagnostic route of CS should not be unbalanced only toward the research of AF (1).

We think that most of them may be due to thromboembolism or vascular risk factors predisposing endothelial damage and thrombus. In the present study we investigated the thromboembolic and cardiovascular risk factors that may explain most of the unknown causes in CS patients and compared with a control group.

In our study we determined only two AF episodes >30 sec. in each group. Moreover in the study group six patients had AF episodes <30 sec. called in current literature as non sustained AF which is higher in CS patients as we demonstrated and indicated in the study of Arsava et al. It was asserted that these episodes may enhance the risk of ischemic stroke (17). However there is no difference between groups in terms of sustained or non-sustained AF.

In the analysis from EMBRACE, the largest AF detection trial in patients with CS, they found that the number of HM detected atrial ectopic activity (AEA) was a potent independent predictor of AF (12). The ratios of AEA or ventricular EA in control and study groups were similar in the present study. We cannot suggest that frequent AEA may be a stroke risk marker independent of causal mechanisms, such as the development of long-lasting AF (7).

In this study, the patients with cardiovascular risk factors; HT, DM and CAD were significantly more prevalent in CS patients. Mean LVEF ratio was significantly lower in the study group, but in normal ranges. Another thromboembolic source; LAD was larger in the study group, but the difference was not statistically different.

Blood LDL, total cholesterol and urea levels were also significantly higher in the study group and HDL was lower. It was demonstrated in logistic regression models that we need larger study and control groups to verify these findings leading us to focus on the thromboembolic etiology of CS.

There were some limitations of our study. Firstly, the number of patients was small and the study design was retrospective. Secondly the duration of HM was not long enough to exclude arrhythmia. Lastly we did not analyze the cTnI levels in those patients.

In routine clinical practice, we suggested that it is hard to apply HM to all CS patients for 30 days. Even in longer HM studies most of the CS etiology still remains unknown. However, in TOAST classification we think that there is no detailed description of a pathway in patients with multiple potential etiological factors, so many patients remain in the cryptogenic stroke group. The extracranial or intracranial atherosclerosis causing < 50% luminal stenosis of the artery supplying the

area of ischemia, large LAD and HT, DM, hypercholesterolemia may be the etiological causes of CS accounting for thromboembolism and cardio-embolism. Large randomized controlled studies are needed to clarify this issue.

As conclusion, cardiovascular risk factors leading thromboembolism, arterial thrombosis, cerebral small vessel disease may be substantially higher within CS population, long-term ECG monitoring may not explain the diagnosis in most of the patients with CS. Lastly we suggested that in the future, the definition and criteria of CS should be updated and reviewed according to new findings.

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