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The significance of Holter electrocardiography in the etiological evaluation of transient ischemic stroke

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Abstract:

BACKGROUND: Transient ischemic attack (TIA) is a common neurovascular disorder associated with a higher risk of stroke within the first 24 h after the first event. Acute cerebral and arterial neuroimaging combined with long-term electrocardiography (ECG) monitoring have been proven to be useful in determining etiology. Cardio-embolism constitutes 20%–26% etiology of TIAs most of them with atrial fibrillation (AF). Investigation of AF after TIA is very important because oral anticoagulants can reduce the risk of subsequent stroke by two thirds.

MATERIALS AND METHODS: The present study included 45 patients suffering from TIA with undetermined source according to the Trial of Org 10172 in Acute Stroke Treatment criteria; the control group (n = 45) was selected from the patients admitted to cardiology outpatient clinic with nonspecific complaints without cerebrovascular and/or cardiovascular disease. All patients underwent echocardiography and 24 h Holter ECG monitoring (HM).

RESULTS: There was no significant difference between the patient group and the control group in terms of age and gender. Cholesterol, low-density lipoprotein and urea levels, left atrium diameters and the incidence of hypertension, coronary artery diseases, and AF were significantly higher in TIA group ($P < 0.05$). In the results of HM, there were six patients with AF in the study group, and in the control group, there was no patients with AF ($P = 0.03$).

DISCUSSION AND CONCLUSION: In acute phase of TIA, 24 h HM is important for determining the etiology and selecting an appropriate treatment that can protect patients from subsequent strokes.

Keywords:

Holter electrocardiography, transient ischemic attacks, undetermined source

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Introduction

Transient ischemic attack (TIA) is a common neurovascular disorder associated with a higher risk of subsequent stroke ranges from 9% to 20% within 3 months, with the highest risk in the first 2 days.[1,2] Because most strokes occur during a 2-day time interval after a TIA, it is important to identify the etiology of TIA and initiate therapy as quickly as possible so as to prevent patients from a disabling stroke.[1] Therefore, about 80% of recurrent strokes are preventable, if early evaluation and treatment are performed.[2]

Acute cerebral and arterial neuroimaging, combined with long-term electrocardiography (ECG) monitoring have been proven to be useful in determining the etiology. Large artery atherosclerosis is the most common cause in TIA etiology with a highest risk of recurrent stroke.[2] In addition, cardio-embolism constitutes 20%–26% etiology of TIAs most of them with atrial fibrillation (AF).[3]

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Ischemic stroke can be prevented in 67% of patients with AF using anticoagulant treatment; therefore, the detection of AF has a great clinical value.[4] Investigation of AF after TIA is vital because oral anticoagulants (OACs) can reduce the risk of subsequent stroke by two-thirds.[3]

Guidelines for the management of stroke patients recommend ≥24 h Holter ECG monitoring (HM) after stroke to determine paroxysmal AF. Even after HM, there are still strokes or TIAs with undetermined sources and may be related with missed AF.[5,6]

However, in a large stroke registry, it was indicated that only one-third (30.6%) of consecutive patients with a first acute ischemic stroke or TIA admitted to stroke centers received the 24 h HM within a month of their attack. Less than 20% received HM in the acute phase (within the 1st week after stroke).[6] We think that all patients admitted with TIA should receive 24 h Holter ECG to reduce undetermined etiology.

In this study, we want to demonstrate the incidence of AF or paroxysmal atrial fibrillation (PAF) in patients with TIA in the acute phase by utilizing 24 h HM and emphasize the importance of determining AF in patients with TIA.

Materials and Methods

Study population

We reviewed all hospitalized patients with the diagnosis of TIA in the Neurology Service between March 2015 and January 2017 retrospectively.

All recruited patients were older than 45 years. Patients admitted with ischemic stroke, cerebral hematoma, lacunar infarcts, hypoglycemia, hypoxemia, seizures or other disorders causing hemiparesis (e.g., brain tumors or multiple sclerosis) were excluded. The study included 45 patients presented with anterior or posterior system TIAs and after routine evaluation those with undetermined source according to Trial of Org 10172 in Acute Stroke Treatment criteria; Patients with ≥70% stenosis of internal carotid arteries, intracranial atherothrombotic disease or lesions in the distal vertebrobasilar arteries, those with a source of cardiac or aortic embolism and arterial dissections were excluded from the study.[7]

Control group (n = 45) was recruited from the patients admitted to cardiology outpatient clinic with nonspecific complaints such as chest pain, vertigo, syncope or effort dyspnea without any valve pathologies, heart failure, arrhythmia, coronary artery disease (CAD) and cerebrovascular diseases and who underwent 24-h HM, transthoracic echocardiography (TTE).

In order to diagnose TIAs with undetermined source, brain imaging (cranial and diffusion magnetic resonance [MR] imaging), computed tomography or MR angiography, TTE and HM were performed. Through TTE, left ventricle ejection fraction (LVEF) and left atrium diameter (LAD) of all patients were measured. A cardiologist reviewed 24-h HM results of all patients independently.

Hypertension (HT), diabetes mellitus, CAD, chronic renal failure, LAD, Holter ECG results and LVEF were compared among groups. Routinely studied blood laboratory tests, low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, triglycerides, hemoglobin, platelets, urea, and creatinine were also noted and compared.

This study was approved by the local ethics committee (January 19, 2016/decision no: 15), and written consents were taken from all participants.

Holter electrocardiography

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

Laboratory tests

Following a 8-h 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, and total cholesterol) and also erythrocyte sedimentation rate, C-reactive protein levels were analyzed.

Statistical analyses

All data were analyzed using the Statistical Package for the Social Sciences, software version 23.0, for Windows (SPSS; Chicago, IL, USA). Categorical variables were compared with the Chi-square test, and numeric variables were compared with ANOVA and Student t-test between the groups. $P < 0.05$ was accepted to indicate statistical significance. Binary logistic regression analysis was performed for the risk factors.

Results

There was no significant difference between the patient group (mean age: 56.62 ± 15.10) and the control group (mean age: 54.66 ± 16.01) in terms of age and gender (22 male in TIA group and 28 male in the control group). The mean NIHSS score on admission was 2.84 (minimum:

1 maximum: 5) and ABCD2 score mean value was 3.46 (minimum: 1 maximum: 6) in patients with TIA.

Cholesterol, LDL, and urea levels were significantly higher in TIA group ($P < 0.05$). In addition, the LADs were significantly higher in the study group (0.00). Mean value of LVEF was higher in the control group, but the ejection fraction percent values were all in normal ranges [Table 1].

The incidence of HT, CAD, and AF was significantly higher in the TIA group ($P < 0.05$). There were no significant differences between other vascular risk factors. The results of binary logistic regression analyses were shown in the last column. As the number of CAD and AF are "0" in the control group, 95% confidence interval EXP (B) values were not able to be calculated [Table 2].

There were six patients with PAF or AF in study group, in the control group, there were no patients with AF, the difference was significantly meaningful ($P = 0.03$). Two patients had non sustained AF lasting <30 s. There were not any significant differences in terms of other cardiac rhythms among groups [Table 3].

Table 1: Comparison of numeric parameters

Parameters	TIA group (*n*=45)	Control group (*n*=45)	*P*
Age	56.62±15.10	54.66±16.01	0.55
Cholesterol	211.06±44.26	192.53±45.49	0.05
LDL	133.22±33.27	113.75±33.63	0.00
HDL	45.46±10.08	48.71±10.27	0.13
Triglyserid	153.91±79.14	163.28±87.29	0.59
Hgb	13.03±1.67	13.11±1.27	0.78
Plt	255.91±77.55	257.68±114.70	0.93
Urea	42.57±24.48	32.15±12.38	0.01
Creatine	1.10±0.61	1.03±0.81	0.65
LAD	37.51±6.04	33.42±5.46	0.00
LVEF	58.44±2.57	60.26±1.99	0.00

TIA: Transient ischemic attack, LAD: Left atrium diameter, LVEF: Left ventricle ejection fraction, Plt: Platelet, Hgb: Hemoglobin, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Table 2: Comparison of vascular risk factors

Parameters	TIA group (*n*=45)	Control group (*n*=45)	*P*	95% CI EXP(B)	
				Lower	Upper
Gender (male)	22	28	0.20	0.68	3.64
HT (n)	32	17	0.00	1.31	9.77
DM (n)	13	7	0.12	0.54	6.16
CAD (n)	11	0	0.00	0.00	
CRF (n)	3	2	0.64	0.05	8.84
Holter ECG (AF)	6	0	0.03	0.00	

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CRF: Chronic renal failure, ECG: Electrocardiography, AF: Atrial fibrillation, CI: Confidence interval, TIA: Transient ischemic attack

Table 3: Holter electrocardiography monitoring results

Cardiac rhythm	TIA group (*n*=45)	Control group (*n*=45)	*P*
AF/PAF	6	0	0.03
AEA/VEA	29	31	0.65
Normal sinus	10	14	0.34

AF/PAF: Atrial fibrillation/paroxysmal atrial fibrillation, AEA/VEA: Atrial ectopic activity/ventricular ectopic activity, TIA: Transient ischemic attack

Discussion

HM has been increasingly utilized in patients with stroke and TIA as a routine investigation for detecting occult PAF.[8,9] AF can be occult or paroxysmal and especially PAF can only be determined through long-term HM. Current guidelines recommend ≥24-h HM, if cardio-embolism is suspected or the etiology of stroke is undetermined despite routine examination.

In a meta-analysis, Sposato *et al*. analyzed 50 studies including 11.658 cases and determined 12.2% new-onset AF diagnosed during the hospitalization through admission ECGs, serial ECGs or HM. Admission ECG alone revealed AF in 7.7% of patients, further AF was detected in 10.7% of patients underwent HM after discharge, but these studies mostly included patients with ischemic stroke, only a minor proportion of patients were with TIA.[10,11] In this meta-analysis, the utility of routine HM in patients with definite stroke or TIA is higher than expected. According to these results, more patients can be treated with OACs and more recurrent strokes can be prevented.[8,10]

In the present study, AF was significantly more common in patients with TIA than the control group, AF was determined in 13.3% of TIA patients underwent 24 h HM. This proportion is higher than estimated. In order to compare the difference among patients without TIA or stroke, a control group was selected from the patients admitted to cardiology outpatient clinic with nonspecific complaints consecutively. There was no patient with AF in the control group.

Despite our findings and meta-analysis, in clinical practice, the investigation of AF generally depends on cardiac history and admission ECG in TIAs, many patients with TIA either do not receive 24-h HM during hospitalization or after discharge, using long term HM in patients with TIA is very rare, even ECHO is performed only in about half of patients with TIA and usually after discharge. Because the hospitalization of patients with TIA in stroke units and centers is tends to be shorter in clinical practice. Although there are current guidelines managing diagnostic examination for the determination of AF in patients with stroke or TIA, the utility of extensive cardiac evaluation and HM in patients with TIA have not been investigated specifically.[3]

Thereby, the underutilization of HM causes an over diagnosis of stroke events as cryptogenic; an under diagnosis of AF, an inadequate anticoagulant treatment

and lower possibility of secondary stroke prevention,[6] and hereby more recurrent strokes. To reduce the ratio of missed AF in patients with TIA, there needs to be a guideline for the routine clinical practice. The only specific definition in England's national guidelines for TIA management recommend all high-risk patients (ABCD2 score ≥4) to be examined with further cardiac evaluation within 24 h of onset of symptoms and all other patients within 7 days, even in the UK routine practice of cardiac evaluation in TIA is unclear.[3,12]

Furthermore, cardio-embolic or AF-related strokes have a poor prognosis as >50% of the survived patients with a severe morbidity, and the ratio of recurrence can be up to 12%/year. Unfortunately, AF is often asymptomatic in approximately 30% of patients contributing under the diagnosis of AF. In addition, PAF is intermittent and has been demonstrated as asymptomatic in up to 90% of the patients; hence, it is more difficult to determine PAF.[13]

In summary, the sensitivity of standard ECG or serial ECG is lower to detect AF or PAF than 24 h HM which provides the opportunity of determining previously unrecognized AF or PAF in the routine clinical practice.[14,15]

As demonstrated in our study, the left atrial (LA) diameters were bigger in the study group. Although LA diameter was not associated with stroke recurrence, patients with AF had significantly larger LA diameters compared to patients without AF. The diameters and functions of LA detected by ECHO may predict AF in patients with TIA and may be used to manage AF monitoring strategy in patients with TIA.[16,17]

On the other hand, serum cholesterol, LDL, and urea levels were higher, and HT and CAD were more prevalent in the study group. These are known vascular risk factors of stroke and TIA.

Our study has some limitations; firstly, it is retrospective, and second, the study population is not large enough. Further, larger randomized controlled studies are needed to clarify the duration and utility of HM in TIAs with undetermined etiology.

Conclusion

Consequently, in patients with TIA in the acute phase, ≥24 h HM is important for determining AF/PAF and selecting an appropriate treatment which can prevent subsequent strokes that cause disability and mortality.

As demonstrated in our study, the incidence of AF is higher than expected in patients with TIA. Further, higher serum cholesterol, LDL and urea levels, and higher incidence of vascular risk factors such as HT and CAD are determined in the study group. In addition, LA diameters were also higher in patients with TIA supporting that LAD is not associated with stroke recurrence, but patients with AF had significantly larger LA diameters compared to patients without AF.

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Conflicts of interest
There are no conflicts of interest.

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