Paroxysmal atrial fibrillation in young cryptogenic ischemic stroke: A 3-week ECG Holter monitoring study

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Background. Atrial fibrillation is known very frequent cause of ischemic stroke. Undetected paroxysmal atrial fibrillation (PAF) is thus often considered a possible cause of cryptogenic ischemic stroke (CIS). The aim of this prospective study was to detect PAF using ECG Holter monitoring and determinate whether prolongation of the Holter monitoring to 3 weeks would increase the detection rates of PAF in young CIS patients ≤ 50 years.

Methods. The study set consisted of IS patients ≤ 50 years enrolled in the HISTORY (Heart and Ischemic STroke Relationship study) study (NCT01541163). CIS was defined according to the TOAST criteria including the absence of ultrasonographic or angiographic signs of atherosclerosis, vasculitis or dissection. Admission ECG, serum levels of high sensitive Troponin T (hs TnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP), markers of thrombophilia, transoesophageal echocardiography (TEE) and 24-hour ECG-Holter monitoring were performed in all patients. In case of negative 24-h ECG Holter, an additional 3-weeks monitoring was done.

Results. Of the 105 enrolled patients ≤ 50 years, 95 (90%) were identified as cryptogenic (49 males, mean age 39.1 ± 8.2 years). All CIS patients had normal admission ECG. In total, PAF was detected in 9 (9.5%, 95% CI: 3.5% - 17.8%) patients; in two during 24-h ECG Holter and in seven during 3-weeks Holter monitoring. Patients with PAF had more frequently elevated admission hs TnT and NT-proBNP levels ($P = 0.0001$).

Conclusions. PAF was detected in 9.5% of young CIS patients and 3-weeks ECG Holter monitoring increased the detection rate.

Key words: cryptogenic ischemic stroke, paroxysmal atrial fibrillation, ECG Holter monitoring, young stroke

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INTRODUCTION

The cause of ischemic stroke (IS) remains often unclear (cryptogenic) despite an extensive diagnostic panel¹. In young patients, cryptogenic ischemic stroke (CIS) represents more than one third of all ischemic strokes²⁻⁴. Embolism due to cardiac abnormalities, particularly atrial fibrillation (AF), represents a very frequent cause of IS in these patients^{3,6}, therefore undetected paroxysmal AF (PAF) is often considered the cause in CIS patients⁷⁻⁸. Patients with AF (including transient or paroxysmal forms) have a high risk for recurrent IS and oral anticoagulation is highly effective in secondary prevention^{9,10}. Thus, a diagnostic effort should be made to detect PAF in patients with IS. A standard ECG has a limited ability to detect PAF, while a continuous ECG Holter monitoring may increase it^{7,8,11,12}.

The frequency of AF in young IS patients has not been studied in depth, however undetected AF is considered a cause of IS. A few previous studies have shown the presence of AF in approx. 3-4% of young IS patients up to 50 years at the time of hospitalization^{3,4,13}. In spite of

the greater rate of detected AF using a 24-h ECG Holter monitoring¹⁴, the presence of AF in young patients may be underestimated due to insufficient detection of PAF.

The aim of this prospective study was to report detection rates of PAF using an ECG-Holter monitoring in young CIS patients ≤ 50 years and determine whether prolongation of continuous monitoring (up to 3 weeks) would increase the detection rates of PAF. We assumed our findings might contribute to discussion about an optimal duration of ECG-Holter monitoring for PAF detection in young CIS patients.

MATERIALS AND METHODS

Patients

The study set consisted of consecutive acute IS patients ≤ 50 years, who were enrolled in the prospective single-center observational HISTORY (Heart and Ischemic STroke Relationship study) study registered on ClinicalTrials.gov (identifier NCT01541163) between years 2011 and 2014 (ref.¹⁵). In all patients, brain ischemia was confirmed on

CT or MRI. Patients unable or unwilling to give consent were excluded. The study protocol was in compliance with the current Declaration of Helsinki and study was approved by the Ethics Committee of the hospital.

Data collection and clinical evaluation

Medical history, baseline characteristics, epidemiologic data, and risk factors were recorded in all patients at admission or during hospitalization. Stroke severity was quantified using the National Institutes of Health Stroke Scale (NIHSS) at admission. All patients underwent following diagnostic work-up: 1) brain CT or MRI on admission and 24 h later 2) serial laboratory samples, 3) admission ECG, 4) ultrasound of cervical and cerebral arteries within first 48 h, 4) transoesophageal echocardiography (TEE), 5) 24-h ECG Holter monitoring.

The serial laboratory panel used contained the following samples: 1) standard laboratory panel, 2) basic coagulation parameters and standard screening panel of thrombophilia including genetic screening, 3) serum cardiac markers ≤ 12 h after stroke onset (N-terminal pro-brain natriuretic peptide [NT-proBNP], high sensitive Troponin T [hs TnT]), 4) serum levels of glycosylated hemoglobin and lipids < 60 h after stroke onset. The details and normal values of the specific methods have been published¹⁵.

CIS was defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification¹⁶ without presence of any known stroke cause including any ultrasonographic or angiographic signs of atherosclerosis, vasculitis or dissection.

All admission ECGs were evaluated by blinded cardiologists (M.H., M.F.). All patients with CIS and negative 24-hour ECG Holter monitoring underwent subsequent 3-week ECG-Holter monitoring. A 24-hour monitoring was performed using a Holter monitor Philips-Zymed DigiTrack plus/DigiTrack XT (Philips, Netherlands) and a 3-weeks monitoring using a Holter monitor MDT Vitaphone Loop 3100 BT (Vitaphone GmbH, Germany). All records from 3-week Loop Holter were processed in an external medical data transfer (MDT) center and evaluated by specially trained and blinded cardiologists. The presence of AF was defined as at least 1 period of > 30 seconds' duration of an absolute arrhythmia without detectable P waves and without a pattern more consistent with an alternative diagnosis^{17,18}.

Statistical analysis

SPSS software (version 15.0; SPSS Chicago) was used for statistical analysis. Normality of distribution was checked using the Shapiro-Wilk test. All parameters with non-normal distributions are presented as means $\pm$ SD, medians, and interquartile ranges. All tests used an α -level of 0.05 for significance.

RESULTS

In total, 652 consecutive acute IS patients were enrolled in the HISTORY study and 105 (16%) of them

were ≤ 50 years (54 males, 41.2 ± 8.1 years). In this patient cohort, two (1.9%) patients presented with AF on admission. Eight (7.6%) patients had other known cause of IS (3 patients had a symptomatic arterial dissection, one patient had a symptomatic severe stenosis of the internal carotid artery, one patient had a severe dilatational cardiomyopathy with thrombus in the left ventricle, one patient had an artificial valve replacement with insufficient anticoagulation, two patients had a confirmed severe thrombophilia; one patient had detected resistance of activated protein C and the other had antiphospholipid syndrome [lupus anticoagulant]). The remaining 95 (88.7%) patients (49 males, 39.1 ± 8.2 years) were identified as cryptogenic and comprised the study set.

In total, PAF was detected in 9 (9.5%, 95% CI: 3.5% - 17.8%) CIS patients during ECG-Holter monitoring. The demographic and baseline characteristics of these patients are shown in Table 1. There was no significant difference between PAF and CIS patients in these parameters.

A 24-hour ECG-Holter was started after a median of 5.3 days (interquartile range 4.1 - 8.3 days) after admission. 3-week ECG-Holter was performed after a median of 42 days (interquartile range 25 - 96 days) after admission. No interruptions of Holter monitoring and no significant technical difficulties occurred and patients tolerated long-term monitoring. Paroxysmal AF was detected in two patients during 24-h ECG-Holter and in another 7 patients during 3-week monitoring. Mean time from start of 3-week monitoring to the first detection of PAF was 11.5 ± 3.4 days.

Patients with detected PAF had elevated admission serum levels of hs TnT and NT-proBNP (Table 2) significantly more frequently than patients without detected AF (56% vs. 2% and 56% vs. 3.5%, $P=0.0001$). Two (22%) patients with detected AF had elevated both cardiac markers. There was no difference between groups in terms of a patent foramen ovale (PFO) with an evident right-left shunt on TEE (Table 2).

In all patients with detected PAF, oral anticoagulant therapy was initiated.

DISCUSSION

The results of our study showed a clear trend towards higher rates of detected PAF with a prolongation of ECG-Holter monitoring also in young stroke patients, while this trend was reported previously in elderly population only^{7,11,19}. Nevertheless, the rate of detected PAF (9.5%) in our study was lower than the previously reported rates achieved during 7-day Holter monitoring (12-13%) (ref.^{7,20}). This difference may be due the fact that our study population was selected from patients with CIS only and was substantially younger (≤ 50 years). Previously reported age-dependent yields of screening for undetected AF in stroke patients suggested this explanation²⁰. In the recently reported randomized EMBRACE (Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event) study, PAF was detected in 16.1% of patients over 55 years with cryptogenic stroke using a 30-day ECG-Holter monitoring¹².

Table 1. Demographic and baseline stroke characteristics of CIS patients and PAF patients.

Characteristics	CIS	PAF	<i>P</i>
N	86	9	
Age (yrs), mean $\pm$ SD	40.3 $\pm$ 6.2	43.1 $\pm$ 3.2	0.903
Males	44 (51 %)	5 (56 %)	1.000
Baseline NIHSS (Median + interquartile range)	9 (3-18)	8 (4-16)	0.986
Stroke in anterior circulation	61 (71 %)	6 (67 %)	1.000
History of prior TIA/stroke	2 (2.3 %)	0	1.000
Hypertension	7 (8.1 %)	0	1.000
Diabetes mellitus	1 (1 %)	0	1.000
Hyperlipidemia	12 (14 %)	1 (11%)	1.00
Coronary artery disease	0	0	1.000
Peripheral artery disease	0	0	1.000
Smoking	21 (24 %)	2 (22 %)	1.000
Alcohol abuse	2 (2 %)	0	1.000
Systolic blood pressure (mmHg)	135 $\pm$ 7	132 $\pm$ 9	1.000
Diastolic blood pressure (mmHg)	69 $\pm$ 14	74 $\pm$ 11	0.978
IV thrombolysis	36 (42 %)	6 (67 %)	0.205
Endovascular treatment	12 (14 %)	1 (11 %)	1.000

IV = intravenous, NIHSS = National Institutes of Health Stroke Scale, SD = standard deviation, TIA = transient ischemic attack

Table 2. Laboratory parameters and TEE findings of CIS and PAF patients.

	CIS patients	PAF patients	<i>P</i>
NT-proBNP > 125 ng/L	3 (3.5 %)	5 (56 %)	0.0001
Hs TnT > 0.014 μ g/L	2 (2 %)	5 (56 %)	0.0001
Creatinine > 90 μ mol/L	2 (2 %)	0	1.000
Baseline serum level of GLU > 5.6 mmol/L	46 (54 %)	5 (56 %)	1.000
Glycosylated hemoglobin > 40mmol/L	2 (2 %)	0	1.000
Baseline serum level of CH > 5.0 mmol/L	25 (29 %)	2 (22 %)	1.000
Left atrial diameter (mm) (mean $\pm$ SD)	35 $\pm$ 5	36 $\pm$ 8	1.000
Left ventricular ejection fraction (%)	55	60	0.989
PFO with significant right-left shunt	25 (29 %)	2 (22 %)	1.000
Other defect of atrial septum	3 (3 %)	0	1.000

CH = cholesterol, CIS = cryptogenic ischemic stroke, GLU = glucose, hs TnT = high sensitive Troponin T, NT-proBNP = N-terminal pro-brain natriuretic peptide, PAF paroxysmal atrial fibrillation, PFO = patent foramen ovale, SD = standard deviation, TEE = transoesophageal echocardiography

In young IS patients < 50 years, previous studies showed a frequency of AF up to 5% (ref.^{2,3,20-22}). The use of a 24-h ECG Holter and a prolonged ECG Holter monitoring (up to 7 days) did not increase this low frequency in these patients^{7,20,24,25}. In our study, the prolongation of Holter monitoring up to 3 weeks increased substantially the detection rate of PAF with the mean time of 11.5 $\pm$ 3.4 days from the start of monitoring to the first detection of PAF.

In our study, the loop recorder was used for the detection of PAF. This type of recorder detects arrhythmias triggered by a patient only. Thus the detection rate may be limited in case of an asymptomatic episode of AF. Continuous telemetric or implantable monitors may provide a more accurate PAF detection. These devices are able to record user-defined, automatic and patient-

activated episodes of AF or other arrhythmias²⁶. However, in the recently published randomized CRYSTAL AF (Cryptogenic Stroke and Underlying AF) study, the rate of detected PAF did not exceed 10% during a 6-month period of continuous monitoring²⁷.

Paroxysmal AF represents the same risk for a recurrent IS as a permanent form of AF (ref.²⁸). Moreover, the frequency of episodes of PAF increases over time and AF may become persistent²⁹. The duration of AF is considered necessary for thrombus formation, however the TEE-based studies showed that short intervals of AF may also generate a thrombus^{30,31}. Although PAF has been defined as an episode of AF in duration > 30 s (ref.^{17,18}), we assume that shorter periods of AF (< 30 s) may be also relevant for detection of PAF. We agree with the suggestion that very short AF episodes may be associated

with longer undetected AF episodes of sufficient duration, which result in thrombus formation and subsequent embolization¹⁹.

The presence of PFO with evident right-left shunt on TEE was registered only in one patient with detected PAF. Regarding the fact that the thrombus formation due to AF occurs in the left atrium and ventricle primarily³¹, we suggest there is no relevance of PFO in CIS patients with detected PAF. Moreover, the relevance of PFO as a risk factor for IS has been still discussed. Although PFO is more prevalent in IS patients, recently published results from the PC Trial showed no significant benefit of the PFO closure for patients with CIS (ref.³²). Similarly, results from the RESPECT trial were negative in the primary intention-to-treat analysis. However, the additional results from the per-protocol analysis suggested a certain benefit of closure³³.

The elevation of serum hs TnT and NT-proBNP in our PAF patients may correspond to the reported findings that elevation of hs TnT is associated with AF and that NT-proBNP was found to be a robust predictor of AF, especially in younger patients^{34,35}. Thus we suggest the serum elevation of hs TnT and NT-proBNP might help to better identify IS patients with undetected PAF, in whom a diagnostic effort with a sufficient length of ECG-Holter monitoring is needed for detection of PAF.

The study has limitations. A single center study design with a small sample size was used. Nevertheless, the incidence of IS in young patients is generally low and most previously reported studies with young CIS patients < 50 years had similar sample sizes. The interval from stroke onset to start of 24-h and 3-week ECG Holter was relatively longer. For a 3-week monitoring, the loop recorder with a limited ability to record arrhythmias was used. Thus we cannot exclude the possibility of a higher detection rate if continuous telemetry or implantable recorders were used.

In conclusion, AF (including its transient or paroxysmal forms) represents a high risk for recurrent IS, thus a greater diagnostic effort to detect AF is required, especially in younger patients with unclear cause of IS. The prolongation of ECG-Holter monitoring up to 3 weeks increased the detection of PAF in these patients.

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