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2015.11.14 Received: Accepted: 2015.12.16 Published: 2016.03.02 Panagiota Christia Authors' Contribution: AEF 1 1 Department of Internal Medicine, Jacobi Medical Center/Albert Einstein College of Study Design A E 1 Ioanna Katsa Medicine, New York, NY, U.S.A. Data Collection B 2 Department of Neurology, Jacobi Medical Center/Albert Einstein College of Lenore Ocava F 2 Statistical Analysis C Medicine, New York, NY, U.S.A. FF 1 Robert Faillace Data Interpretation D Manuscript Preparation E Literature Search F Funds Collection G **Corresponding Author:** Panagiota Christia, e-mail: Panagiota.christia@nbhn.net Conflict of interest: None declared Female, 80 Patient: **Final Diagnosis:** Stroke Symptoms: Weakness • left sided **Medication: Clinical Procedure: Echocardiogram** Naurology Specialty: **Objective:** Unusual clinical course **Background:** Stroke is the major cause of disability and the fifth leading cause of death in the United States. In 30-40% of strokes the etiology remains uncertain or unknown. Identifying the cause of a cerebrovascular event offers the opportunity for an intervention that may decrease the risk of future stroke and thus prevent the resultant impairment. **Case Report:** We report the case of an 80-year-old African American woman with a prior right middle cerebral artery stroke, who presented to the hospital with new left-sided weakness and was found to have a new right-sided frontal lobe infarct. Twenty-four hour Holter monitoring performed during this hospitalization and prior 24-h electrocardiogram (ECG) recording did not reveal an arrhythmia. However, the patient was found to have an isolated

> episode of atrial fibrillation (AF) during an echocardiogram as part of the evaluation for stroke etiology. **Conclusions:** AF is an important and treatable cause of recurrent stroke and needs to be ruled out by thorough evaluation before the diagnosis of cryptogenic stroke is assigned. Despite meticulous diagnostic work-up, many strokes caused by paroxysmal AF remain undetected and longer ECG monitoring (>24 h) may be required.

MeSH Keywords: Atrial Fibrillation • Electrocardiography • Stroke

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Background

Stroke is the fifth leading cause of death in the United States, with 795 000 patients experiencing a cerebrovascular event every year [1,2]. While 1 out of 6 strokes are attributed to atrial fibrillation (AF), 1 out of 4 has no identifiable cause after a basic work-up has been completed [3]. However, based on observational studies [4-6] and recently published randomized controlled trials [3,7,8], undiagnosed AF might be the cause of a significant number of strokes of undefined etiology. Current guidelines recommend 30-day cardiac monitoring for patients with a cryptogenic stroke or transient ischemic attack (TIA) [9]. Our case report underscores the importance of prolonged arrhythmia surveillance using either a monitor that is embedded in the sub-cutaneous tissue of a patient or mobile cardiac outpatient telemetry (MCOT) [10] in patients with cryptogenic or possible cardioembolic strokes, especially those who have underlying risk factors for paroxysmal AF, such as hypertension or known cardiac disease.

Case Report

An 80-year-old African American woman presented to the emergency department of our hospital with sudden-onset left-sided weakness. She was at her baseline until the afternoon prior to admission, when she was found on the floor by family members. She denied any associated symptoms such as shortness of breath, chest pain, palpitations, headache, dizziness, or loss of consciousness.

Her past medical history included hypertension, hyperlipidemia, heart failure with reduced ejection fraction (left ventricular ejection fraction=40%), prior right middle cerebral artery (MCA) stroke, and knee osteoarthritis. The right MCA stroke occurred a year prior to the current hospitalization, with residual cortical sensory loss in the left hand. It was characterized as cryptogenic because no cause was identified. She had a 24-h Holter monitor, which did not reveal any arrhythmias, her duplex of the carotid arteries was negative for stenosis of the extracranial carotid arteries bilaterally, and her echocardiogram was not suggestive of patent foramen ovale. The patient was discharged to subacute rehabilitation on aspirin, clopidogrel, and statin. Seven months after her first stroke she was admitted to another hospital with an upper gastrointestinal (GI) bleed. At that time clopidogrel was discontinued. Three months prior to her last admission she was hospitalized in another facility for left arm weakness and bluish discoloration of the limb. She was found to have an occlusion of the ulnar artery and was placed on a heparin drip, with resolution of her neurological symptoms. At that time she also had an echocardiogram, 24-h electrocardiographic telemetry monitoring, and carotid ultrasound, without any identifiable source of cardio-embolism.

Her past surgical history included total left knee replacement, hysterectomy for fibroids causing metrorrhagia, and carpal tunnel surgery. She was not allergic to any medications. She never smoked or used alcohol or drugs. Both her parents had hypertension. She was living alone, had a health aide assist her 5 days a week, and was ambulating with a walker. On admission she was on aspirin, a statin, furosemide, and metoprolol.

On physical examination she was found to be in no acute distress, and she was alert and oriented to self and place but not to time. Her neurological exam was significant for flaccid left-sided hemiplegia, left upper motor neuron facial paresis, decreased sensation to light touch on the left hemibody, leftsided neglect, and anosognosia. Her lower extremities were swollen bilaterally. Her cardiovascular exam was unremarkable, her abdomen was benign, and she had some fine bibasilar crackles on lung auscultation but not elevated jugular vein distention (JVD). She was afebrile, her heart rate was 69/min, and her blood pressure 160/102 mmHg.

Investigations

Her ECG on admission was unremarkable, without evidence of ischemia or any arrhythmias. A computed tomography (CT) of the brain revealed a new right anterior frontal lobe infarct along with the old infarct at the posterior aspect of the frontal lobe. MRI of the brain demonstrated multifocal acute infarcts involving the right hemisphere on the background of an old MCA infarct. A Doppler of the carotid arteries did not demonstrate any evidence of carotid stenosis, and a Holter monitor was placed for 24 h without evidence of arrhythmias. Her echocardiogram revealed diffuse hypokinesis with low normal ejection fraction (EF) of 40% and no evidence of patent foramen ovale; however, she had an isolated episode of AF identified on EKG recording during her echocardiogram.

Treatment

The patient was started on anticoagulation and was discharged to subacute rehabilitation on warfarin and a high-intensity statin. She did not have recurrent cerebrovascular accident (CVA) events.

Discussion

Ischemic stroke remains one of the leading causes of disability and death in the United States [1,9]. In 30–40% of the cases no cause is identified after routine evaluation and these strokes are classified as cryptogenic [4,11,12]. Atrial fibrillation is a well-studied and recognized cause of ischemic stroke; however, given the paroxysmal and often asymptomatic nature of the disease, its diagnosis remains challenging because it might not be identified on routine and serial ECGs, telemetry monitoring, or even after 24-h ECG Holter monitor recordings [3,5]. Diagnosis of AF in a patient who sustained an ischemic stroke is of utmost importance and has therapeutic implications [3,4] because initiation of anticoagulation with either warfarin or one of the new oral anticoagulants, such as dabigatran, rivaroxaban, or apixaban, has been clearly shown to reduce recurrent cardio-embolic events and strokes [13]. Without identification of AF as an etiologic factor for stroke, treatment will be limited to antiplatelet therapy [3,9,14].

Approximately 10% of patients admitted with an acute ischemic stroke will be newly diagnosed with AF during the same hospital admission. Another 10-15% of these patients will also be found to have at least 1 episode of AF if they are followed electrocardiographically for 30 days [3,7,15]. In a recently published randomized controlled trial (the CRYSTAL-AF trial) by Brachman et al, 8.9% of the patients who were followed with an insertable cardiac monitor for 6 months had an episode of AF after a cryptogenic stroke compared to 1.4% in the control group [7]. After 12-month follow-up, AF was detected in 12.4% of the patients monitored compared to 2% in the control group [7]. By 36 months, 30% of the patients that had implantable cardiac monitoring were found to have AF compared to only 3% in the control group. In another retrospective study that investigated the detection of AF by 30day cardiac event monitoring, it was shown that 20% of patients with cryptogenic stroke or TIA were found to have AF even though initial basic work-up did not reveal any cause [5]. Based on the above findings, the 2014 guidelines from the American Stroke Association on prevention of recurrent stroke recommend prolonged rhythm monitoring (30 days) for patients with an ischemic stroke if the cause remains unknown after the basic work-up is complete [9].

In our case the patient had evidence of possible thromboembolism considering her prior stroke and the episode of limb arterial thrombosis; however, given the lack of a documented cardiac source of embolus her stroke could not be classified as cardioembolic based on the TOAST classification. Interestingly, she fulfils criteria for a new entity described as "Embolic Stroke of Undetermined Source [ESUS]", described in 2014, as she had a non-lacunar stroke without proximal arterial thrombosis or cardioembolic source. Hart et al. argue that patients with ESUS should be anticoagulated given the high risk of recurrence. However, randomized controlled studies are needed to validate this recommendation. In the WARSS trial – the only randomized controlled trial comparing anticoagulation with antiplatelet therapy – there was a significant reduction in recurrent ischemic events in patients with cryptogenic strokes whose CT showed an embolic topography (18% vs. 12%, 95% CI 0.4–1.2). In this era of newer anticoagulants that carry lower risk of intracranial bleeding while offering excellent anticoagulation, 2 large randomized trials comparing dabigatran (RESPECT-ESUS) and rivaroxaban (NAVIGATE) with aspirin in this population are currently underway.

Our patient had the good fortune to have an isolated episode of AF while she was having an echocardiogram, which was identified on routine concomitant ECG recording observed during the time of the echocardiogram, allowing the diagnosis of AF. The current case report aims to underscore the importance of the current recommendation for prolonged rhythm monitoring when the history is concerning for a cardioembolic cause of stroke. Even in the absence of documented episodes of AF during the 30-day monitoring, current guidelines leave the decision for prolonged monitoring (>30 days) to the discretion of the treating physician [9]. Considering the high rates of AF detection at 36 months in the study by Brachman et al. [7], extension of monitoring time in patients with recurrent thromboembolic strokes appears a reasonable approach. Moreover, AF as a cause of stroke has been associated with more disability and worse neurological outcomes [3,16,17] compared to other causes of stroke, making early detection of unidentified AF in a patient presenting with cryptogenic stroke of utmost importance.

Whether 30-day EKG recording is the optimum duration based on cost-effectiveness is an issue that merits further investigation [4,11,18,19]. Randomized controlled trials comparing different durations of rhythm monitoring in this patient population, having as endpoints rate of AF detection and cost-effectiveness, are awaited in the near future [8].

Conclusions

Paroxysmal atrial fibrillation is frequently an undetectable, silent, and treatable cause of stroke. Twenty-four hour ECG monitoring after a CVA event might not be long enough as part of the work-up for identifying AF as a possible cause; therefore, for patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged EKG monitoring (30 days) for AF is reasonable. The MCOT (mobile cardiac outpatient telemetry) system has been proven to have 99% sensitivity and 96% positive predictive value for identifying atrial fibrillation lasting >30 s and could be used in an outpatient setting for patients with cryptogenic strokes.

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