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Journal of Cardiology & Current Research

Review Article

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Proposal of a study protocol for cryptogenic stroke in a tertiary hospital

Abstract

It has been estimated that approximately 20% of ischemic strokes have a cardioembolic origin and that the cause is not detected or that there may be more than one in 9-25% of them. An adequate diagnostic process of ESUS (embolic strokes of undetermined source) would allow optimization of antithrombotic treatment. Our objective with the publication of this protocol is to propose the essential diagnostic tests to make the diagnosis of ESUS and the optimization of patients who can benefit from prolonged cardiac monitoring.

Keywords: TIA, transient ischemic attack; ESUS, embolic stroke of undetermined source; PFO, patent foramen ovale, AST, aspartate aminotransferase; CT, computed tomography, MRI, magnetic resonance imaging

Volume 16 Issue 2 - 2023

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Received: April 12, 2023 | **Published:** April 21, 2023

Introduction

This protocol refers to those patients who have suffered an episode of acute cerebral ischemia, in the form of established stroke or TIA (transient ischemic attack), classified as cryptogenic stroke, that is, those patients in whom after performing a complete etiological study (Figure 1), it is not possible to establish the exact etiology of the stroke.

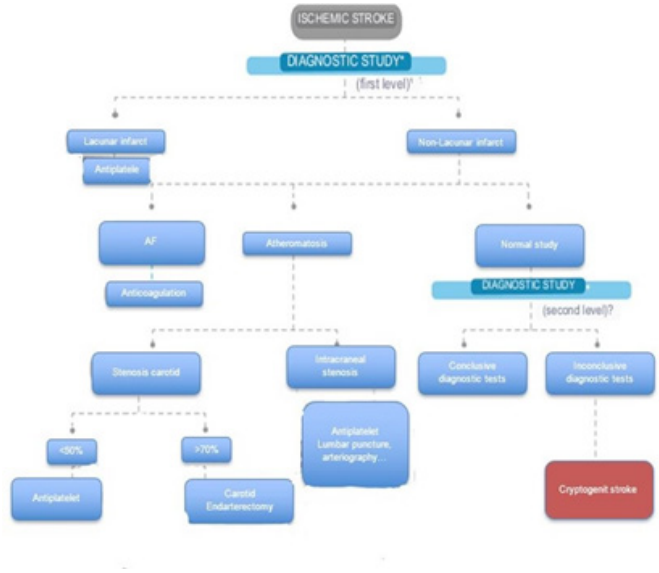

Figure 1 Diagnostic protocol.

Once the complete etiological study has been carried out, for those patients whose diagnostic tests have resulted negative, prolonged monitoring of cardiac rhythm will be required. In a significant percentage of patients with cryptogenic stroke, the cause of the stroke is hidden atrial fibrillation, and its detection is essential to identify the cause of the stroke and to adopt a highly effective preventive strategy such as anticoagulation.[1–5]

Within cryptogenic strokes, prolonged cardiac monitoring is especially indicated in the subgroup called ESUS (embolic stroke of undetermined source) characterized by:

1. To define a stroke as ESUS, a minimum of 24 hours of cardiac frequency monitoring is required.
2. Ischemic stroke detected in CT/MRI of NON-lacunar etiology (<1.5cm in CT or <2cm in MRI).
3. Absence of extracranial or intracranial atheromatosis that originates a stenosis greater than 50% in the arteries that supply the ischemic area.
4. There are no major cardioembolic sources (Table 2).
5. Unusual causes of stroke have been ruled out (dissection, thrombophilia, arteritis, vasospasm/migraine, toxins, etc.).[6–12]

Prior to prolonged monitoring, it is necessary to rule out infrequent causes of paradoxical embolisms associated with PFO (patent foramen ovale), pulmonary shunt and venous thrombosis (especially important in hypercoagulability states associated with cancer). Keep in mind that, according to the 2022 ESO Guidelines, any 55-year-old patient with PFO and a diagnosis of cryptogenic stroke would benefit from prolonged cardiac monitoring implantation.

Selection of cardiac monitoring method

1. Continuous Monitoring during Hospital Admission: Whenever available, patients will remain monitored during their admission for a minimum of 24hours, preferably 48-72hours.
2. 24h Holter: Only for those patients who cannot be monitored during their admission or access via consultation without hospital admission.
3. Insertable Holter Reveal: Patients in whom AF has not been detected during admission (or during Holter 24h). In these cases, an individual patient assessment will be performed, and those who meet any of the following criteria will be candidates for implantation

1. CHA2DS2-VASC>5.
2. Left atrial dilation (>45 mm).
3. Non-lacunar cerebral infarctions in different vascular territories.
4. Other atrial rhythm disorders.
5. Presence of spontaneous echo contrast or flow slowing in the atrial appendage.

The following patients will not be considered candidates for the present protocol

1. Patients in whom detection of AF is not going to modify the treatment regimen: patients with current oral anticoagulation treatment; or patients who cannot receive anticoagulation treatment.
2. Patients with a life expectancy of less than 1 year.
3. Patients for whom in-person or remote device follow-up will not be possible.
4. Patients without a caregiver and with disability according to the Rankin scale ≥4, or with cognitive or neuropsychological sequelae that impede the correct development of the protocol.
5. Patients with a known etiology of TIA or stroke (based on neuro/cardio/vascular imaging information) (Figure 1).

The finding of these minor abnormalities will classify the patient's experienced cerebral infarction as "possible" cardioembolic as long as there are no other potential causes of cerebral infarction. Aortic arch atheromatosis should be evaluated in the context of atherothrombotic mechanism, not cardioembolic Tables (1 & 2).

Classification adapted from SSS-TOAST, based on the annual risk of stroke > 2% (major sources) or <2% (minor sources).

These predictors should be taken as support to assess the risk of atrial fibrillation, they are not necessary criteria to request prolonged cardiac monitoring (Table 3).[13–19]

Table 1 Diagnostic Study Levels

1* Diagnostic study 1st level	2° Diagnostic study 2nd level
- Cranial TC and/or briain MRI	- Transesophageal echocardiogram
- Electrocardiogram	- immunological study, serology and thrombophilia study, genetic study.
- Doppler AST, CT angiography and or trunk angioMR supra-aortic and transcranial	
- Transthoracic echocardiogram	
- Complete analysis including glycated Hb and lipid profile	
- ECG holter monitoring 24/48h)	

Table 2 List of Cardioembolic Sources

Major cardioembolic sources
Atrial fibrillation, including paroxysmal atrial fibrillation
Persistent atrial flutter
Valvular prostheses, mechanical or biological
Recent myocardial infarction (<4 weeks)
Old myocardial infarction (> 4 weeks) associated with ejection fraction <28%
Left ventricular or atrial thrombi
Left atrial myxoma
Papillary fibroelastoma
Infectious or non-infectious endocarditis
Dilated cardiomyopathy
Symptomatic congestive heart failure with ejection fraction <30%
Sick sinus syndrome
Rheumatic mitral or aortic valve disease
Patent foramen ovale
Atrial septal aneurysm, associated or not with patent foramen ovale
Left ventricular aneurysm without thrombus
Isolated spontaneous echo contrast (without mitral stenosis and without atrial fibrillation)
Mitral annular calcification, including severe calcification

Citation: Jiménez DEB, Rodríguez JV, Merino DD, et al. Proposal of a study protocol for cryptogenic stroke in a tertiary hospital. *J Cardiol Curr Res.* 2023;16(2):43–46. DOI: 10.15406/jccr.2023.16.00576

Table 3 Predictors for the detection of atrial fibrillation

Risk Factor	Criterion	Risk ratio	Reference
Age	> 75 years	4	Andrade J et al.[1] Thijs VN et al.[2]
Age	> 60 years	2	Favilla CG et al[3] Thijs VN et al.[2]
Brain image	Multilocular infarcts from previous cortical or cerebral infarction.	5.6	Favilla CG et.[3]
Ejection fraction	< 40%	3,6	Miller DJ et al.[4]
Atrial dilation	> 45 mm	3,6	Poli S et al.[5]
Ventricular extrasystoles	> 360/24 horas	3,9	Thijs VN et al al.[2] Kochhäuser S et al.[6] Gladstone DJ et al.[7]
Atrial tachycardia	>20 successive rhythms /24 hours	2,7	Poli S et al.[5]
NT-proBNP	>360 ng/l	5,7	Svennberg E et al.[8] Rodriguez-Yanez M etal.[9]

ANNEX 1: Etiological Classification of Ischemic Stroke, Study Group of Cerebrovascular Diseases of the SEN (adapted from that of the ad hoc committee of the SEN. Cerebrovascular Diseases Study Group (A. Arboix et al., 1998 and 2002).

Atherothrombotic Ischemic Stroke (Due to large artery atherosclerosis)

Medium or large-sized infarction, with cortical or subcortical topography and carotid or vertebrobasilar location, which meets one of the following two criteria:

I. A. Presence of atherosclerosis with stenosis: ≥50% stenosis of the vascular lumen diameter or occlusion of the extracranial artery or a large intracranial artery (middle cerebral, posterior cerebral or basilar trunk), in the absence of another explanation.

II. B. Atherosclerosis without stenosis: the presence of plaques with a stenosis of less than 50% in the middle cerebral, posterior cerebral or basilar artery, in the absence of another etiology. At least two of the following cerebrovascular risk factors must be present: person over 50 years old, hypertension, diabetes mellitus, smoking or hypercholesterolemia.

Cardioembolic ischemic stroke

Medium or large-sized infarction, usually with cortical topography, for which there is evidence (in the absence of an alternative etiology) of any of the following embolic heart diseases: the presence of an intracardiac thrombus or tumor, rheumatic mitral stenosis, aortic or mitral prosthesis, endocarditis, atrial fibrillation, sinoatrial node disease, acute myocardial infarction in the previous three months with or without left ventricular aneurysm or extensive akinesia, or presence of global cardiac hypokinesia or dyskinesia regardless of the underlying heart disease.

Small artery occlusive disease (lacunar infarction)

Small infarction (diameter less than 1.5cm) in the area of a cerebral perforating artery, which usually causes a lacunar clinical syndrome (pure motor hemiparesis, pure sensory syndrome, sensory-motor syndrome, ataxic hemiparesis or clumsy-hand dysarthria) in a patient with a history of hypertension or other cerebrovascular risk factors, in the absence of another etiology.

Ischemic stroke of unusual etiology

Small, medium, or large-sized infarction, with the cortical or subcortical location in the carotid or vertebrobasilar territory in a patient in whom atherothrombotic, cardioembolic, or lacunar origin has been ruled out. It may be caused by systemic diseases (metabolic disorders, coagulation disorders, connective tissue diseases, myeloproliferative syndrome, or infectious processes) or other causes such as cerebral venous thrombosis, migraine, septal aneurysm, arterial dissection, fibromuscular dysplasia, arteriovenous malformation, vasculitis, or iatrogenic causes.

Cryptogenic ischemic stroke

Medium to large infarction, cortical or subcortical location, in the carotid or vertebrobasilar territory, in which, after an exhaustive diagnostic study, atherothrombotic, cardioembolic, lacunar, and unusual subtypes have been ruled out.

Ischemic stroke of undetermined origin due to the coexistence of causes

Medium to large infarction, cortical or subcortical location, in the carotid or vertebrobasilar territory, in which more than one possible etiology coexists.

Ischemic stroke of undetermined origin due to insufficient study

Medium to large infarction, cortical or subcortical location, in the carotid or vertebrobasilar territory or in which the cause has not been determined due to an incomplete or insufficient study.

Conclusion

Optimizing treatment after a stroke is essential to reduce the risk of recurrences. There are certain patients with ESUS who could benefit from anticoagulation, such as those with a possible origin cardioembolic. Since AF constitutes the etiology most frequent cardioembolic stroke, it is their detection is very important to start, as soon as possible, the timely treatment. Longer monitoring in patients with a greater number of risk factors would increase the chances of diagnosing AF and, therefore, the potential benefit of anticoagulant treatment.

Funding

None.

Acknowledgments

None.

Conflicts of interest

Author declares there are no conflicts of interest towards publication of this article.

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