Chapter 8

Cryptogenic Stroke

Rubens J. Gagliardi and Vivian D.B. Gagliardi

Additional information is available at the end of the chapter

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Abstract

Introduction: To emphasize the importance of this kind of stroke, to focus on secondary stroke prevention and to recognize that the etiology of stroke is fundamental for proper prevention. In this chapter, the history of this stroke subtype is described and its actual specific denomination: embolic stroke undetermined source (ESUS).

Objectives: To define "cryptogenic stroke," the main characteristics and therapeutics proposals.

Discussion: The following main characteristics of this kind of stoke are presented here: the incidence in several countries and international statistics, the specific physiopathology of this kind of stroke, the different methods for its correct diagnosis and the importance of exhaustive cardiac investigation, the main cause of ESUS with special focus in the importance of paroxysmal atrial fibrillation. The new therapeutic options (anticoagulants versus antiplatelets) are presented and discussed based on the recent trials.

Conclusion: Importance of correct definition of the stroke etiology for its appropriate secondary prevention; would anticoagulation be better than antiaggregation for adequate prevention? We look forward to the results of recent trials in this field.

Keywords: stroke, cryptogenic stroke, cerebral embolism, embolic stroke of undetermined source (ESUS), anticoagulants, atrial fibrillation

1. Introduction

Cryptogenic stroke is a kind of stroke without a known cause, with a negative screening for a definite cause, such as cardioembolism, atherothrombosis, arterial dissection, and lacunar

stroke [1]. This term was introduced in 1988 [1] and has gained importance because of the need to clarify the stroke cause for its effective treatment and secondary prevention. The definition of the stroke etiology is of great importance since it is directly related to its prognosis and treatment and guides the secondary prevention strategy.

Known atherothrombotic stroke responds reasonably well to antiplatelet (AG), and cardioembolic stroke responds better to anticoagulant than to AG, and therefore, there should be a careful etiological definition. The risk of recurrence of a cryptogenic stroke is high [2, 3], because it surely is not being adequately prevented. Recently, the term ESUS ("embolic stroke undetermined source") has been used to describe these cases [4], since most of these cases of cryptogenic strokes are embolic with an undetermined the source of embolism.

1.1. Etiologic stroke classification

There are several classifications and scales to help determine the etiologic diagnosis of stroke. The TOAST (Trial of Org 10172 in Acute Stroke Treatment) Subtype Classification System [1] has been widely used and divides the acute ischemic stroke in five subtypes according to their causes: atherosclerosis of large arteries (carotid and cerebral), cardioembolic, occlusion of small vessels (lacunar), certain other causes (e.g., thrombophilias), and undetermined cause (cryptogenic stroke). The prevalence of cryptogenic strokes varies from 20 to 40% of all subtypes of stroke in most studies [2, 3].

Recently, researchers have discussed deeply on why the incidence of this event has remained high over the years. Often the investigation is incomplete, but in many cases, this investigation is adequate, and yet it is not possible to identify the cause of the stroke. In these cases, the first suspicion should be for a transient or reversible mechanism [4, 5].

2. Physiopathology

Many different pathophysiological mechanisms have been proposed as possible causes for a cryptogenic stroke [4]:

- Cardioembolic sources, such as mitral annular calcification, aortic valve stenosis, aortic valve calcification, atrial asystole and sick sinus syndrome, atrial high rate episodes, atrial appendage stasis with reduced flow velocities or spontaneous echodensities atrial structural abnormalities, atrial septal aneurysm, Chiari network, moderate systolic or diastolic dysfunction (global or regional), ventricular non-compaction, endomyocardial fibrosis, covert paroxysmal atrial fibrillation.
- Cancer-associated emboli: covert nonbacterial thrombotic endocarditis, tumor emboli from occult cancer.
- Arteriogenic emboli: aortic arch atherosclerotic plaques, cerebral artery non-stenotic plaques with ulceration.

– Paradoxical embolism: patent foramen ovale, atrial septal defect, pulmonary arteriovenous fistula.

The cardioembolic mechanisms as possible genesis of cryptogenic stroke have been deeply discussed [4, 6], believing that they are often are not recorded, either for lack of relevant research or the characteristic paroxysms (as in paroxysmal atrial fibrillation), which may make this arrhythmia not evident at the time of investigation. The cardioembolic causes has been the subject of deep and extensive discussions in recent years, with special attention to atrial fibrillation (AF) and patent foramen ovale (PFO), due to its high prevalence in the general population.

2.1. Atrial fibrillation

Atrial fibrillation is an example of a transient cause that corresponds to 10% of all stroke and is estimated to be responsible for 50% of the cryptogenic stroke. The AF is paroxysmal in 30% of patients with stroke and therefore is often not identified within the first days or weeks after a stroke, as seen in several trials. It is known that the investigation of AF can present false negatives because of the possible paroxysmal rhythm, which suggests the need for long-term monitoring. Several studies have proven that long-term monitoring [7–9] for atrial fibrillation increases the chances of detecting paroxysmal AF. Several devices have been proven for this, including outpatient mobile telemetry and the outpatient transtelephonic monitoring, implantable loop recorder. Culebras et al. [8] describe in the 2014 consensus of the American Academy of Neurology evidence of the work of the last decade analyzing the effectiveness of these mechanisms to detect AF (ECG, Holter, event loop, outpatient telemetry / hospital, outpatient transtelephonic monitoring ECGs series) and showed a tendency that the higher monitoring time is related to the higher detection rate of the AF.

For example, the study CRYSTAL AF [9] in 2014 studied the presence of AF in patients with transient ischemic attack (TIA) or stroke cryptogenic for 6 and 12 months, using a insertable cardiac monitor, a previously validated device for AF detection which is implanted in the patient and records an electrocardiographic lead. This study showed that when compared to control groups, AF was observed in 8.9% of patients within 6 months of evaluation, compared to 1.4% in control patients ($p < 0.001$) and 12.4% of patients 12-month assessment, against 2.0% in the control group ($p < 0.001$). Thus, it is clear that patients with cryptogenic stroke should have a more comprehensive research, in addition to ECG and Holter, since there is evidence that device is most effective in detecting paroxysmal AF.

A potential biomarker for determining the risk of AF occurring after cryptogenic stroke could be the dosage of brain natriuretic peptide (sBNP) serum levels [10], which are high in AF, and therefore could be useful for the monitoring of these patients; however, this is not consensual yet and needs further confirmation.

2.2. Patent foramen ovale

Another situation often associated with cryptogenic stroke is the presence of patent foramen ovale (PFO). This is a common anatomic abnormality in the general population—an estimated

prevalence of 26% [11]. The PFO appears to be a risk factor for stroke in young adults; one meta-analysis showed that patients younger than 55 years have higher rates in the presence of PFO than the control population, and the same does not occur in patients older than 55 years [11].

The presence of PFO may lead to cerebral ischemia by several mechanisms [6]:

– Paroxysmal embolism of peripheral venous system;
– Embolization of thrombi in the atrial septum;
– Embolization of thrombi formed by paroxysmal arrhythmias.

The presence of PFO may be associated with the occurrence of atrial septal aneurysm (ASA), Chiari network, or other atrial septal defects. The presence of PFO and its relationship to stroke can be difficult to determine. The SPARC study [12] suggests that the presence of an isolated PFO, adjusted to age and comorbidities, is not considered a risk factor for cerebrovascular events; however, the risk of stroke in patients with PFO and ASA is four times higher than in patients without ASA. Other features such as the right-left shunt at rest and septal hypermobility are related to higher risk of stroke than isolated PFO [13].

The diagnosis of PFO is performed by echocardiography; evaluation by transcranial Doppler can aid the diagnosis in a first approach as it can demonstrate right-left communication (shunts) when detecting microembolic signals; however, this rating is less sensitive to small PFOs and does not evaluate cardiac structure anatomically, so that echocardiography is still the method of choice [6]. The gold standard investigation for PFO is the Transesophageal echocardiography (TEE) [6].

There is no consensus regarding the treatment of PFO, and its approach includes the use of antiplatelet agents, anticoagulants, closing by percutaneous, or surgical closure device. Clinical treatment with warfarin or acetylsalicylic acid (ASA) is indicated as secondary prophylaxis in cryptogenic stroke in patients with PFO—there is no evidence of superiority of one treatment compared to another. There is still no clear benefit of PFO closure therapy because it is not yet clear which the patient that best benefits from this approach, nor what kind of approach would be superior [14, 15].

3. Etiological investigation

There is no consensus about the etiological investigation stroke, but recent studies cite that the investigation should include performing computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, 12-lead ECG, cardiac monitoring for 24 h (Holter), transthoracic echocardiogram, screening for thrombophilia in patients younger than 55 years, angio-CT/angio MRI/or cervical and intracranial digital angiography, ultrasonography Doppler of cervical, and vertebral arteries.

In cases where the cause for the stroke is unknown despite adequate research, it is suggested to expand the investigation of possible cardioembolic events, given their greater frequency in

the general population. To this end, it is suggested performing transcranial Doppler, transesophageal echocardiography-TEE (which is the gold standard for cardiac anatomic evaluation), and an increased time heart rhythm study (greater than 24 h), as discussed previously. The TEE should also evaluate the presence of aortic arch atheroma, as cryptogenic stroke patients have an increased prevalence of atherosclerotic disease of the aorta, which could lead to an embolic stroke [16]. The transcranial Doppler may detect microembolic signs [17], which could be related to PFO or pulmonary arteriovenous fistula for example.

Some authors also suggest including pelvic magnetic resonance venography in patients with cryptogenic stroke and PFO, as deep vein thrombosis could be a source of paradoxical embolism in these patients [18].

There seem to be a statistically significant clinical and radiological difference between patients with cryptogenic stroke and PFO, AF, and aortic arch atheroma. Ryoo et al. [16] described in one study that patients with PFO had healthy vascular risk and more posterior circulation involvement; AF-related events present with higher NIHSS scores and larger lesions than other groups; and aortic arch atheroma was related to small lesions in multiple territories. Although this needs further studies, these patterns could help guiding the investigation.

In young patients with cryptogenic stroke and already investigated for thrombophilias, supplementation with genetic study to thrombophilic disease appears to have no benefit [15]. Studying this situation showed no statistically significant increase in the prevalence of Stroke related to genetic polymorphisms in young patients investigated for thrombophilic causes, including evaluation of factor V gene Leiden, prothrombin gene, angiotensin-converting enzyme gene, gene of 5,10-metilenotetrahidrofolate-reductase (MTHFR), endothelial nitric oxide synthetase gene (ecNOS) activating factor gene of plasminogen activator (tPA) inhibitor factor-1 gene of plasminogen activator (PAI-1), and HaeIII polymorphism of β-fibrinogen gene [19].

4. Treatment

Considering that the correct secondary stroke prevention depends on the precise knowledge of the etiology of the stroke, it is very important to define it. Unfortunately, until now, there is no definition about the best management of secondary prevention in cryptogenic stroke.

The consensus of the American Stroke Association/American Heart Association 2008 specifically recommends antiplatelet indication for the treatment of cryptogenic stroke. However, more recent consensus does not specifically comment on managing this stroke subtype [4].

There are few studies analyzing this issue. The WARSS study [20] showed that in a sample of patients with cryptogenic stroke, the rate of recurrence of the event or death was statistically lower in patients who used warfarin (target INR between 1.4 and 2.8) than in patients receiving acid acetylsalicylic (ASA) at a dose of 325 mg/day. Recently, some authors as Hart et al. [4] suggest the introduction of anticoagulant treatment for secondary prophylaxis in patients with undetermined etiology stroke. Ongoing trials such as the RES-PECT ESUS [21]

studies and NAVIGATE ESUS [22] are comparing the use of acetylsalicylic acid to the use of novel oral anticoagulants and should help to determine the choice of treatment in the future (**Table 1**).

Trial	Drug	Started
RES-PECT ESUS [21]	Dabigatran vs. ASA	2015
NAVIGATE ESUS [22]	Rivaroxaban vs. ASA	2015

ASA, acetylsalicylic acid.

Table 1. Ongoing trials comparing ASA vs. the new oral anticoagulants in ESUS patients.

Author details

Rubens J. Gagliardi[1,2] and Vivian D.B. Gagliardi[3*]

*Address all correspondence to: rubensjg@apm.org.br and viviandbg@gmail.com

1 Neurology, School of Medical Sciences, Santa Casa de Sao Paulo, Sao Paulo, SP, Brazil

2 Brazilian Academy of Neurology, Brazil

3 Federal University of São Paulo, Sao Paulo, SP, Brazil

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