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Review

Cryptogenic stroke. A non-diagnosis[☆]

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ABSTRACT

The term cryptogenic stroke refers to a stroke for which there is no specific attributable cause after a comprehensive evaluation. However, there are differences between the diagnostic criteria of etiological classifications used in clinical practice. An improvement in diagnostic tools such as advances in monitoring for atrial fibrillation, advances in vascular imaging and evidence regarding the implication of patent foramen oval on the risk of stroke specially in young patients are reducing the proportion of stroke patients without etiological diagnosis. We carried out a critical review of the current concept of cryptogenic stroke, as a non-diagnosis, avoiding the simplification of it and reviewing the different entities that could fall under this diagnosis and reviewing the different entities that could fall under this diagnosis; and therefore avoid the same treatment for different entities with uncertain results.

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Palabras clave:

Ictus criptogénico

Monitorización cardíaca prolongada

Placa de ateroma

Foramen oval permeable

Ictus criptogénico. Un no diagnóstico

RESUMEN

El ictus criptogénico se define como aquel para el que no encontramos una etiología. Sin embargo, existe cierta heterogeneidad en los criterios para definir un ictus criptogénico entre las diferentes clasificaciones etiológicas de uso habitual. Los avances en sistemas de monitorización y detección de fuentes cardioembólicas, el avance de las técnicas de neuroimagen para la caracterización de la placa de ateroma, así como la mayor evidencia de la implicación del foramen oval permeable en el riesgo de ictus en pacientes jóvenes, hacen que cada vez menos ictus queden sin un diagnóstico etiológico. Realizamos una revisión crítica del concepto de ictus criptogénico como un «no diagnóstico», resaltando la importancia de realizar un estudio diagnóstico completo, evitando simplificaciones que pueden llevar a agrupar diferentes entidades que, aunque no identificadas, podrían subyacer al ictus criptogénico y, por tanto, a aplicar el mismo tratamiento preventivo a todas ellas, con resultados inciertos.

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Stroke is considered cryptogenic when an etiologic diagnosis is not found.¹ But in clinical practice, a cryptogenic stroke is a hodgepodge containing multiple and different possible causes which were not identified in the etiological study or whose pathogenic role is not sufficiently recognized. These include paroxysmal atrial fibrillation (PAF), patent foramen ovale (PFO), carotid artery atherosclerosis without stenosis or aortic arch atheroma, as well as other less common causes or little known as inflammatory processes, genetic alterations or hypercoagulability, among others.

In addition, depending on the classification used, different diseases can be recognized as causes of a cerebral infarction.

The possible implications of the diagnosis of cryptogenic stroke need to be taken into account, since admitting that we do not know the cause of the stroke suffered by the patient also involves the uncertainty about the risk of recurrence, which some series estimate that can reach up to 30% of the cases.² It also influences the efficacy of secondary prevention, since the specific treatment is not applied to the cause, since we do not know it. Another aspect, not sufficiently valued, is that not identifying the cause of the stroke can compromise the patient's confidence in the medical team and also condition a lower adherence to preventive treatment. On the other hand, another implication of the diagnosis of cryptogenic stroke is the need to expand the study with high resolution neuroimaging to study the pathology of the extra- or intracranial arterial wall as well as the prolonged heart rhythm monitoring.

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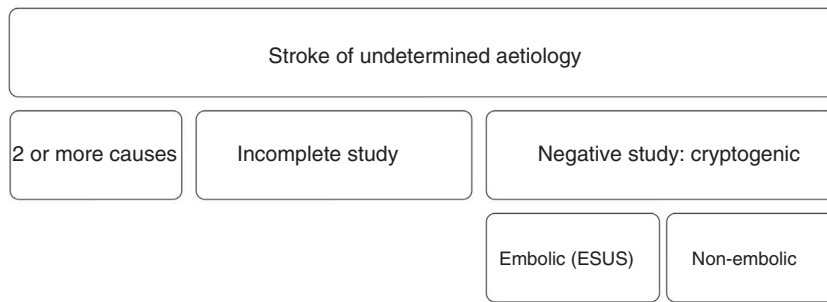


Fig. 1. Progression of the cryptogenic stroke concept. ESUS: *embolic stroke of undetermined source*.

In this review we analyze the concept of cryptogenic stroke considering the different classifications, delving into the different diagnostic techniques for the identification of the underlying cause and exposing the trends of its therapeutic approach.

Concept: definition and progress

The different etiological classifications for cryptogenic stroke have improved as knowledge about cerebrovascular disease has expanded, with the aim of minimizing the number of stroke patients in whom the aetiology is unknown³ (Fig. 1). Normally, a stroke is considered cryptogenic when no cause is found for it, when 2 or more possible causes coexist or when a complete diagnosis is not made⁴⁻⁷ once the diagnostic process has been completed. The first classification is the *Trial Org-10172 Acute Stroke Treatment* (TOAST)⁴ classification, designed for use in clinical trials. It was validated in only 20 cases, of which 7 were classified as cryptogenic strokes, showing a moderate observer agreement (kappa index between 0.42 and 0.54).^{5,8-10} The main drawback of its use in clinical practice is that a large number of strokes are left undiagnosed, since minor cardioembolic sources or arterial stenosis <50% are not considered causes. This is why the *Stop-Stroke Study-TOAST* (SSS-TOAST) classification was created, which incorporated improvements in the use of neuroimaging and epidemiological criteria to support the most probable diagnosis, which contributed to reduce the percentage of strokes classified as cryptogenic down to 4% and modified the classification of some entities such as aortic arch atheroma that becomes part of the cardioembolic group, and eliminates mitral valve prolapse and left ventricular segmental wall motion abnormalities.¹¹ This classification included the development of an *on-line* tool to facilitate the etiological diagnosis in clinical practice, changing its name to *Causative Classification System* (CCS).⁶ Classification of atherosclerosis; small-vessel disease; cardiac pathology; other causes (ASCO) later modified as ASCOD to include the category of arterial dissection, was created with the aim of indicating the most probable aetiology of a stroke based on the available evidence from the diagnostic tests performed and the characteristics of the patient, without omitting any of the other possible entities present in the patient. Five categories are considered (atherothrombotic, small vessel, cardioembolic, dissection and others) and, within these groups, levels of diagnostic certainty are established based on the possibility that the identified entity is the direct cause of the stroke and the degree of existing evidence that said disease is the cause of the stroke.^{12,13} The novelty of this classification is that the concept of cryptogenic stroke does not exist as such. In this classification, arterial stenosis <50% and aortic arch atheroma are considered as uncertain causes and the presence of PFO as an unlikely cause.^{12,13} However, it is too complex, so its use has not been generalized in clinical practice.

In 2014, the concept of *embolic strokes of undetermined source* (ESUS), which is defined as a non-lacunar stroke detected on computed tomography (CT) or magnetic resonance imaging (MRI),

in the absence of both a stenosis >50% of the vessel that supplies the infarcted area as well as a major cardioembolic cause and after having ruled out other etiologies.¹⁴ Different potential causes of embolism are included within this term, such as minor cardioembolic sources, atherosclerotic plaques <50% of vessel lumen stenosis, aortic arch atheroma and paradoxical embolism due to abnormal communication of the arterio-venous system. However, this construct is not new, since the SSS-TOAST classification includes a section of cryptogenic embolism that includes these potential causes, and, in the ASCOD classification, this type of pathologies has a causal significance assigned based on the evidence of related published studies.^{11,15} In addition, in our opinion, it is a step backwards to include in the same group different aetiologies with different pathogenic basis.

The Cerebrovascular Diseases Study Group of the Spanish Society of Neurology (GEECV-SEN) published a diagnostic classification in 1998¹⁶ which was later updated in 2006. It was designed for clinical practice application, incorporating elements of the TOAST and Lausanne classification.⁷ It includes a cryptogenic stroke category divided into 3 sections: (a) those in which a cause is not found after an exhaustive study, (b) coexistence of 2 aetiologies and (c) that situation in which the study has been insufficient.

The main problem with these classifications is that the same disease, depending on the classification used, can be considered as a cause or not of a cryptogenic stroke (Table 1) and, therefore, the subsequent management of the patient will be different.

For this reason, the need to reserve the cryptogenic term for those cases in which, after an extensive history-taking and adequate complementary studies, no cause is found (a true cryptogenic aetiology) is increasingly evident, completely separating from this group the strokes in which there is a concurrence of several causes or those in which a complete diagnosis is not made (Fig. 2).²

Epidemiology

It is estimated that, in Spain, the percentage of stroke of undetermined aetiology is 23.1%. Of these, almost 65% have been classified as cryptogenic based on an inadequate or insufficient study, 23% due to the combination of several possible causes and only 12% due to the lack of aetiology after an exhaustive diagnostic process (true cryptogenic strokes).¹⁷

Overall, the incidence of cryptogenic stroke varies according to the series. In young patients (15-45 years of age) their incidence varies between 8.3% and 62.4% depending on whether the presence of PFO is considered an aetiology,^{1,18} whereas, in elderly patients, the incidence varies between 20% and 40% when using the TOAST classification.¹ An example of the differences in the estimation of the frequency of cryptogenic stroke based on the etiological classification used is the North Dublin population study, in which the TOAST, ASCO and CCS classifications were compared. In a cohort of 381 patients with a first cerebral infarction, the percentage of cryptogenic strokes was 39% when the TOAST criteria were applied, 26%

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