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Review

Covert atrial fibrillation and atrial high-rate episodes as a potential cause of embolic strokes of undetermined source: Their detection and possible management strategy

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ABSTRACT

Cryptogenic ischemic stroke, defined as stroke of undetermined etiology, accounts for 7–25% of all ischemic strokes. Stroke severity is reported to be less severe than cardioembolic stroke and similar to large-artery atherosclerosis. Because its etiology is believed to be mostly an embolic type, it is often called “embolic strokes of undetermined source” (ESUS). In patients with ESUS, it is of significant importance to seek an embolic source with intensive diagnostic assessment, which mostly originates from the heart. Covert atrial fibrillation (AF) and atrial high-rate episodes (AHRE) detected by cardiac implantable electronic devices are believed to contribute to the pathogenesis of ESUS. AHRE is common not only in device-implanted patients, but also in older patients with cardiovascular risk factors. However, it is unclear whether AHRE is a direct cause or simply a risk marker of stroke. Furthermore, indication of anticoagulation therapy for stroke prevention in patients with AHRE remains undetermined. In this review, we focus on the roles of covert AF and AHRE in the pathogenesis of cryptogenic ischemic stroke or ESUS. Detection of covert AF and AHRE, and possible management strategies are also discussed.

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Introduction

Cryptogenic ischemic stroke is defined as stroke of undetermined etiology. However, the etiology has a high likelihood of being an embolic type. The international working group, hence, presented a likely embolic type of stroke as “embolic strokes of undetermined source” (ESUS) [1,2]. Causes of ESUS include thrombi from the left atrium in atrial fibrillation (AF), the left ventricle, the aortic arch, and carotid arteries, etc. Although clinical AF such as persistent or paroxysmal AF documented by 12-lead electrocardiogram (ECG) or ECG monitoring plays a major role in the pathogenesis of cardioembolic stroke, covert AF including asymptomatic paroxysmal AF and atrial high-rate episodes (AHRE) are believed to contribute to the pathogenesis of ESUS [3,4]. AHRE is defined as atrial tachyarrhythmia episodes with rate >190 beats/min detected by cardiac implantable electronic devices (CIED) [4]. Covert AF and AHRE can be detected by in-hospital monitoring, serial ECG, 24–48 h Holter monitoring, cardiac event recorders, wearable external loop recorders, CIED, and insertable cardiac monitors (ICMs) [4–18]. In this review, we focus on the roles of covert AF and AHRE in the pathogenesis of cryptogenic ischemic stroke or ESUS and discuss their detection and possible management strategies.

Clinical characteristics of cryptogenic stroke and ESUS

What are cryptogenic stroke and ESUS?

Stroke subtype in patients with ischemic stroke is generally determined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [19]. This classification comprises five subtypes of ischemic stroke: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology (cryptogenic stroke). The last subtype includes ischemic stroke patients who have no likely etiology determined despite an extensive evaluation, who do not have an adequate evaluation such as early death after admission, and who have multiple potential causes of stroke without a final diagnosis [19]. Among patients diagnosed with cryptogenic stroke, those having an undetermined etiology despite an extensive evaluation often show embolic pattern by brain imaging. In this context, Hart et al. reported that most cryptogenic strokes are thromboembolic and they introduced the concept of ESUS in 2014 [1]. Consistently, recent studies analyzing thrombi obtained from stroke patients with large-vessel occlusion who underwent thrombectomy demonstrated that the composition of thrombi from cardioembolic and noncardioembolic stroke patients differed significantly: cardioembolic thrombi had higher proportions of fibrin/platelets, fewer erythrocytes, and more leucocytes than noncardioembolic thrombi [20,21]. Most importantly, cryptogenic strokes showed strong overlap with cardioembolic strokes in terms of thrombus histology. These findings strongly indicate that patients diagnosed with cryptogenic stroke despite an extensive evaluation have an embolic source from somewhere, especially from cardiac origin.

Diagnosis of ESUS

Diagnosis of ESUS is achieved after exclusion of lacunar strokes, major-risk cardioembolic sources, and proximal occlusive atherosclerosis, as shown in Table 1. Therefore, diagnostic assessment including brain computed tomography (CT) or magnetic resonance imaging (MRI), 12-lead ECG, echocardiography, cardiac monitoring for 24 h or more with automated rhythm detection, and imaging of both the extracranial and intracranial arteries is of critical

Table 1

Criteria for diagnosis and proposed diagnostic assessment for embolic strokes of undetermined source (ESUS).

Criteria for diagnosis of ESUS
<ul style="list-style-type: none"> Stroke detected by computed tomography (CT) or magnetic resonance imaging (MRI) that is not lacunar Absence of extracranial or intracranial atherosclerosis causing $\geq 50\%$ luminal stenosis in arteries supplying the area of ischemia No major-risk cardioembolic source of embolism^a No other specific cause of stroke identified (e.g. arteritis, dissection, migraine/vasospasm, drug misuse)
Proposed diagnostic assessment for ESUS
<ul style="list-style-type: none"> Brain CT or MRI 12-lead electrocardiogram Precordial echocardiography Cardiac monitoring for ≥ 24 h with automated rhythm detection
Imaging of both the extracranial and intracranial arteries supplying the area of brain ischemia (catheter, MRI, or CT angiography, or cervical duplex plus transcranial Doppler ultrasonography)
Imaging of the proximal aortic arch is not needed; special blood tests for prothrombotic states only if the patient has a personal or family history of unusual thrombosis or associated systematic signs or disorder.
Reproduced with permission from Hart et al. [1].
^a Major-risk cardioembolic sources are permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, recent (<4 weeks) myocardial infarction, left ventricular ejection fraction less than 30%, valvular vegetations, or infective endocarditis.

Table 2

Causes of embolic strokes of undetermined source (ESUS).

Minor-risk potential cardioembolic sources^a
<i>Mitral valve</i>
<ul style="list-style-type: none"> Myxomatous valvulopathy with prolapse Mitral annular calcification
<i>Aortic valve</i>
<ul style="list-style-type: none"> Aortic valve stenosis Calcific aortic valve
<i>Non-atrial fibrillation atrial dysrhythmias and stasis</i>
<ul style="list-style-type: none"> Atrial asystole and sick-sinus syndrome Atrial high-rate episodes Atrial appendage stasis with reduced flow velocities or spontaneous echodensities
<i>Atrial structural abnormalities</i>
<ul style="list-style-type: none"> Atrial septal aneurysm Chiari network
<i>Left ventricle</i>
<ul style="list-style-type: none"> Moderate systolic or diastolic dysfunction (global or regional) Ventricular non-compaction Endomyocardial fibrosis
Covert paroxysmal atrial fibrillation
Cancer-associated
<ul style="list-style-type: none"> Covert non-bacterial thrombotic endocarditis Tumor emboli from occult cancer
Arteriogenic emboli
<ul style="list-style-type: none"> Aortic arch atherosclerotic plaques Cerebral artery non-stenotic plaques with ulceration
Paradoxical embolism
<ul style="list-style-type: none"> Patent foramen ovale Atrial septal defect Pulmonary arteriovenous fistula

Reproduced with permission from Hart et al. [1].

^a Minor-risk sources are more often incidentally present than is the stroke cause when identified in an individual stroke patient, are associated with a low or uncertain rate of initial stroke, and consequently cause-effect relation and management implications are usually unclear.

importance to diagnose ESUS (Table 1). Causes of ESUS are listed in Table 2. A case of ESUS (diagnosed as ESUS at first and finally as cardioembolic stroke; symptomatic paroxysmal AF) is presented in Fig. 1.

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