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Development and refinement of diagnostic and therapeutic strategies for managing patients with cardiogenic stroke: An arduous journey

Fan ZX *et al*. Diagnostic and therapeutic strategies for cardiogenic stroke

Abstract

Cardioembolic stroke, referred to as cardiogenic stroke, is a clinical syndrome in which emboli from the heart pass through the circulatory system and cause cerebral artery embolism and corresponding brain dysfunction. Compared to other subtypes of ischemic stroke, cardiogenic stroke presents with more etiologies, greater severity, worse prognosis, and a higher recurrence rate. In this minireview, we provide new insights into the etiological classification, diagnostic methods, and interventions of cardiogenic stroke.

Key Words: Cardiogenic stroke; Diagnostic methods; Therapeutic strategies

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Core Tip: There are many reviews focused on the diagnosis and treatment strategies of cardiogenic stroke. However, in clinical practice, there are still many problems such as non-standard diagnosis and large differences in treatment measures. In this minireview, we introduce the latest Chinese expert consensus on cardiogenic stroke-based diagnostic criteria and provide some new insights into the etiological classification and interventions of cardiogenic stroke.

INTRODUCTION

Stroke is a disease that can seriously endanger human health. The 2019 Global Burden of Disease study showed that stroke is the second leading cause of death worldwide after ischemic heart disease (11.6% of total deaths), and the third leading cause of death and disability combined (5.7% of total disability-adjusted life years) with ischemic strokes accounting for the majority of strokes (62.4%)[1]. Cardiogenic stroke, also known as cardioembolic stroke, constitutes 20% to 30% of all ischemic strokes. It is a clinical

syndrome in which emboli from the heart pass through the circulatory system and cause cerebral artery embolism and corresponding brain dysfunction[2,3]. With the strengthening of community medical management, atherosclerosis risk factors were significantly reduced (*e.g.*, low-density lipoprotein-cholesterol and blood pressure levels were better controlled than before). As a result, stroke/transient ischemic attacks caused by large-artery atherosclerosis (LAA) and small-vessel occlusion were remarkably decreased; conversely, cardiogenic stroke/transient ischemic attack increased significantly[4]. Compared to other subtypes of ischemic stroke, cardiogenic stroke presents with more etiologies, greater severity, worse prognosis, and a higher recurrence rate[5,6]. Although the diagnosis and treatment of cardiogenic stroke has substantially improved worldwide in recent years, there are still plenty of shortcomings, such as insufficient understanding of this disease and significant differences in treatment strategies[3,4]. Therefore, further strengthening the understanding of the etiological classification, diagnostic methods, and intervention measures of cardiogenic stroke, and uniformly improving the diagnosis and treatment of cardiogenic stroke, have become the top priority in the neurology community.

AS YET CLARIFIED ETIOLOGICAL CLASSIFICATION OF CARDIOGENIC STROKE

According to the definite (or potential) cause of cardiogenic stroke in the A-S-C-O (phenotype) classification and its epidemiological characteristics, the relatively common causes are divided into atrial fibrillation (AF), heart failure, acute coronary syndromes, patent foramen ovale (PFO), rheumatic heart disease, artificial heart valve, infectious endocarditis (IE), dilated cardiomyopathy, and cardiac myxoma. In most cases, the intracardiac wall thrombus, tumor surface thrombus/debris, shedding of vegetations on the valve intima or aortic arch plaque, or paradoxical embolism (derived from veins), underlie the pathogenesis, thereby contributing to the obstruction of cerebral blood vessels[7].

To date, the etiological attribution of cardiogenic stroke remains elusive. Firstly, the boundary between cardiogenic stroke and cryptogenic stroke, especially embolic stroke of undetermined source (ESUS), is blurred. Strokes that do not clearly meet the diagnostic criteria of the known ischemic stroke subtypes are classified as cryptogenic strokes[8,9], and cryptogenic stroke is further defined as ESUS when the clinical and neuroimaging features suggest a distant thrombus origin, the absence of lacunar infarcts, a high-risk source of cardiac embolism, or high-degree stenosis of the responsible vessel at the site of the infarction[10,11] (Figure 1). Regarding the etiology of embolism in ESUS, some cases may originate from arterial-arterial embolism caused by large atherosclerotic plaques in the brain, while other cases may result from some cardiac diseases (*e.g.*, paroxysmal AF, PFO, atrial cardiomyopathy, *etc.*)[3,12], strongly suggesting the existence of an overlap between ESUS and cardiogenic stroke. Hence, for ESUS cases, once the above causes are found through adequate standard evaluation, we recommend that, after multi-disciplinary discussion and confirmation of a cardiac cause, cardiogenic stroke should be considered so that treatment can be initiated as soon as possible. Secondly, there is still controversy over whether aortic arch atheroma (AAA)-related stroke should be classified as cardiogenic strokes, as some clinicians have categorized it as an ESUS subgroup of cryptogenic strokes[12]; however, the latest guideline for the prevention of stroke in patients with stroke and transient ischemic attack from the American Heart Association (AHA)/American Stroke Association (ASA) classified it as a subtype of LAA[13]. In view of this, we propose that while the classification of AAA-related strokes as LAA subtypes may reflect its exact pathogenesis, it is still more appropriate to attribute it to cardiogenic strokes. A strong reason for this is that its mechanisms and clinical manifestations are very similar to those of cardiogenic stroke, and studies have shown that attributing it to cardiogenic stroke has no significant impact on the choice of treatment measures and patient prognosis[14].

URGENCY TO DEVELOP A STANDARDIZED DIAGNOSTIC SYSTEM FOR CARDIOGENIC STROKE

The diagnosis of cardiogenic stroke is frequently made based on its clinical and neuroimaging features, combined with other elements such as vascular and cardiac evaluation. With improvements in disease awareness and detection methods (*e.g.*, long-term electrocardiogram monitoring, echocardiography), the detection rate of cardiogenic stroke has greatly increased in recent years when compared with other subtypes of ischemic stroke[15]. Nonetheless, several lines of clinical and radiological evidence to support cardiogenic stroke have been proposed in this regard since the 1990s[8,16,17], but there are no well-established diagnostic criteria. Additionally, there is also controversy over the specific examination protocol used to identify the etiology of cardiogenic stroke. Finally, there are many other problems, such as inconsistent diagnosis and treatment levels across different medical institutions, misdiagnosis, and mistreatment.

In an attempt to solve these problems, we first proposed new clinical diagnostic criteria for cardiogenic stroke[7]. According to the Chinese expert consensus on the diagnosis of cardiogenic stroke (2019) (Table 1), cardiogenic stroke is categorized into definite cardiogenic stroke, probable cardiogenic stroke, and possible cardiogenic stroke: Definite cardiogenic stroke = 2 of (A) + at least 1 of (B) + C; probable cardiogenic stroke = 2 of (A), or at least 1 of (A) + at least 1 of (B); possible cardiogenic stroke = at least 1 of (A). Clinical validation of the diagnostic criteria is currently underway.

URGENT NEED FOR THE DEVELOPMENT OF A STANDARDIZED AND REFINED INTERVENTION STRATEGY FOR CARDIOGENIC STROKE

Even though the treatment principles of cardiogenic stroke are generally similar to other subtypes of ischemic stroke, more emphasis is placed on anticoagulation therapy. However, when to start or restart anticoagulation therapy and the choice of anticoagulants are mostly based on personal experience, mainly due to the lack of clinical evidence or clinical guidelines. Although the principle of using intravenous

thrombolysis in the acute phase is similar f all subtypes, cardiogenic stroke also has its own specificity. In light of the above issues, the standardization of treating cardiogenic stroke has become an urgent issue which needs to be addressed.

For most stroke patients with AF, the guidelines for the early management of acute ischemic stroke from the 2018 AHA/ASA recommend that oral anticoagulation therapy should be initiated within 4 to 14 d after onset[17]. Nevertheless, in a recent multicenter real-world cohort study, initiation of oral anticoagulation within 4 to 14 d did not significantly reduce the incidence of ischemic and hemorrhagic stroke compared to that initiated within zero to three days[18]. Additionally, regarding the best time to restart oral anticoagulation after acute stroke, Hindricks *et al*[19] suggests that anticoagulation be restarted as soon as possible within 2 wk of onset under the guidance of a multi-disciplinary team (neurologist and cardiologist), in combination with the patient's willingness to treat; however, so far there are no reliable data to support this viewpoint. Regarding the anticoagulant choice, results from four randomized controlled trials involving anticoagulation for stroke or systemic embolism in AF showed that, novel oral anticoagulants (NOACs) are noninferior to warfarin in reducing the risk of stroke or systemic embolism in patients with AF but are safer in terms of adverse reactions, such as risk of intracranial hemorrhage[20-23]. Due to this, we recommend that the risk of hemorrhagic transformation in cardiogenic stroke be taken into account, regardless of indications for anticoagulation (*e.g.,* AF, valvular disease), and treatment should be started or restarted several days to several weeks after the onset of the disease, in consideration of the severity of the disease, the size of the acute cerebral infarction, and the risk of bleeding. It is also necessary to fully consider the faster effect and higher safety characteristics of NOACs compared with warfarin.

With regard to intravenous thrombolysis in cardiogenic stroke, to date, most studies were observational or small sample studies[24-26]; in addition, the consensus on efficacy and adverse reactions such as bleeding were different, mainly owing to differences in inclusion criteria and patient characteristics. It should be kept in mind that the use of intravenous thrombolysis is also limited or complicated under special circumstances,

such as with prior anticoagulation therapy[27-32], recent valve surgery or percutaneous coronary intervention[33,34], and IE-related stroke[35]. Accordingly, a variety of guidelines and expert consensus have provided corresponding individualized treatment advice or recommendations[18,36-38]. Chinese neurologists have also recently reported a case of cardiogenic stroke successfully treated by intravenous thrombolysis with alteplase after reversal of dabigatran by idacilizumab[39]. Hence, for patients with acute cardiogenic stroke, especially those who received anticoagulation before disease onset, we recommend the treatment strategy should be individualized according to the specific situation, and intravenous thrombolytic therapy can be performed after multi-disciplinary consultation to improve patient outcomes.

CONCLUSION

In summary, three major issues are raised in this review: The etiology classification; the boundary between cardiogenic stroke, cryptogenic stroke and ESUS; as well as the attribution of AAA-related stroke all need to be clarified. Regarding the diagnosis, given the fact that currently no well-established diagnostic standard is available, we hence developed a new diagnostic system for cardiogenic stroke. Additionally, we recommend that anticoagulant therapy should be initiated or restarted several days to weeks after the onset of stroke, based on the patients' specific situation, and treatment for acute phase and prevention of recurrent stroke should be actively carried out after multidisciplinary consultation. Despite substantial progress in the diagnosis and treatment of cardiogenic stroke worldwide, there is still a long way to go to address all issues. In particular, the development of a standard protocol for management of the acute phase and recovery phase should be determined as soon as possible. Thus, we look forward to seeing additional evidence-based research, real-world research, and health economics evidence in the future in order for clinicians to gain a more comprehensive understanding of cardiogenic stroke and precise prevention and treatment measures, thereby maximizing the clinical benefit and improving the prognosis of patients.

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