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Case Report

Venous thrombolysis combined with Tirofiban in the treatment of capsular warning syndrome: a case report

Qingqing Wang[1*], Huihui Wang[2*], Hongjing Wang[3], Shaoying Wang[1], Dan Xing[4], Yizhe Meng[5]

[1]Department of Neurology, The Eighth People's Hospital of Hebei Province, Shijiazhuang 050000, Hebei, China; [2]Department of Rehabilitation Medicine, The First Hospital of Hebei Medical University, Shijiazhuang 050023, Hebei, China; [3]Operation Room, The Affiliated Hospital of Qingdao University, Qingdao 266000, Shandong, China; [4]Department of Medical Examination, The Eighth People's Hospital of Hebei Province, Shijiazhuang 050000, Hebei, China; [5]Department of Neurology, Hebei Chest Hospital, Shijiazhuang 050041, Hebei, China. [*]Equal contributors and co-first authors.

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Abstract: Capsular warning syndrome (CWS) is a subtype of transient ischemic attack (TIA), accounting for 4.5% of all TIAs. Due to the absence of cortical signs within 24 hours of onset, CWS is often misdiagnosis or overlooked, making it a rare clinical syndrome with a high disability rate and an increased risk of progressing to cerebral infarction. Clinical practitioners need to pay close attention and provide proactive and effective treatment. Currently, there is no universally recognized treatment standard. This report presents the experience of treating a CWS patient at our hospital with venous thrombolysis combined with Tirofiban.

Keywords: Capsular warning syndrome, Tirofiban, venous thrombolysis

Introduction

Capsular warning syndrome (CWS) is a rare clinical syndrome characterized by recurrent and transient focal neurological deficits, with a high risk of infarction. The exact physiological mechanism of CWS remains unclear, but it is commonly believed to result from impaired hemodynamics in small penetrating vessels of the lesion. In the absence of clear treatment guidelines or established effective treatment methods, thrombolysis and anticoagulation therapy are considered promising options for achieving favorable outcomes. Here, we report a case of intravenous thrombolysis combined with tirofiban for the treatment of CWS. The study was approved by the Institutional Review Board and Research Ethics Committee of the Eighth People's Hospital of Hebei Province and was conducted in accordance with the principles of the Declaration of Helsinki.

Case presentation

A 70-year-old female presented to our neurology department at 06:53:58 on August 8, 2022, with complaints of "episodic right-sided weakness and inability to speak for 1 hour and 36 minutes". During the onset, the patient experienced recurrent episodes of right-sided weakness, speech impairment, facial asymmetry, each lasting for approximately 10 minutes. Upon examination, her vital signs were as follows: heart rate 81 beats per minute, respiratory rate 19 breaths per minute, blood pressure 154/87 mmHg. Neurological examination revealed: clear consciousness during episodes, inability to speak, facial asymmetry, a tongue deviated to the right, muscle strength in the right upper and lower limbs at grade 0, decreased muscle tone in the right limbs, and a positive Babinski sign on the right side. Other relevant findings included an ABCD2 score of 6, national institutes of health stroke scale (NIHSS) score of 13, and a normal Wada water test.

Past medical history: hypertension for 20 years, with the highest recorded blood pressure of 180/100 mmHg, intermittently treated with indapamide tablets without regular blood pres-

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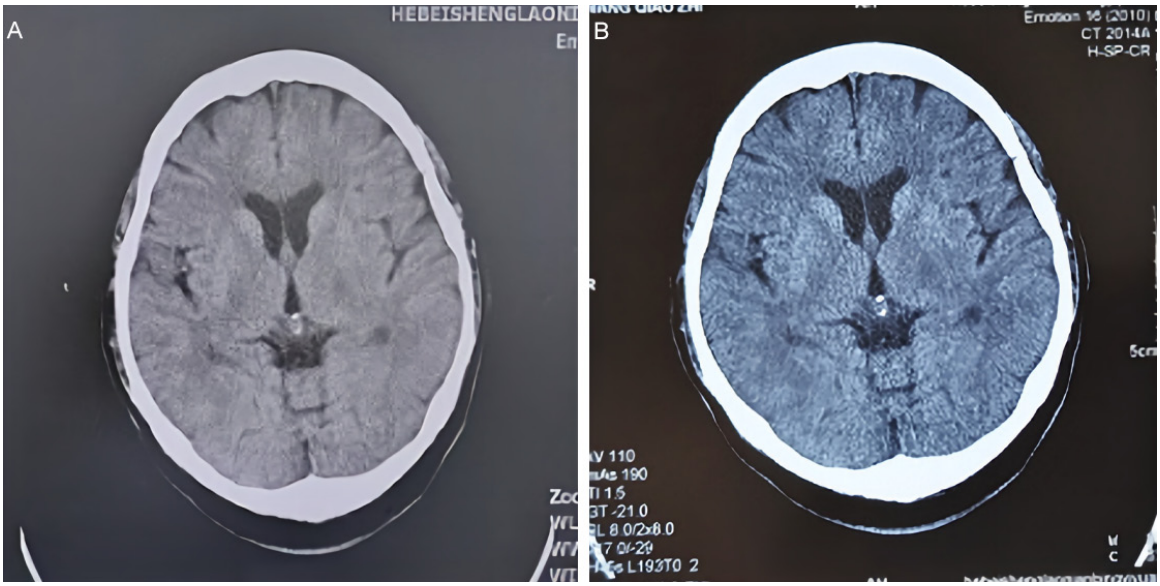

Figure 1. Head computed tomography (CT) showing no significant abnormalities. A: Pre-thrombolysis; B: Post-thrombolysis.

sure monitoring. Type 2 diabetes for over 7 years, managed with extended-release metformin, without regular blood glucose monitoring. An urgent cranial computed tomography (CT) scan showed no significant abnormalities (**Figure 1**).

Laboratory findings: total cholesterol 4.4 mmol/L, low-density lipoprotein 2.78 mmol/L, fasting blood glucose 8.85 mmol/L, glycated hemoglobin 7.4%. electrocardiogram (ECG) showed sinus rhythm with mild ST segment depression in leads V2-V6. Echocardiography revealed aortic valve calcification, mild aortic regurgitation, mild mitral and tricuspid regurgitation, normal left ventricular diastolic function, and ejection fraction (EF) of 60%. Carotid ultrasonography showed bilateral carotid arteries with multiple strong echo plaques. Subclavian artery ultrasound: multiple strong echo plaques in both subclavian arteries, with a thickness of approximately 2.1 mm on the left side and 2.5 mm on the right side at the thickest point. Head magnetic Resonance Imaging (MRI) + diffusion weighted imaging (DWI) + magnetic resonance angiography (MRA): acute left deep periventricular brain infarction, small cerebellar hemisphere softening on the left side, multiple chronic small ischemic lesions in the bilateral parieto-occipital lobes, and MRA imaging consistent with the radiological features of atherosclerotic cerebrovascular disease (**Figure 2**).

Admission diagnosis: 1. Capsular warning syndrome; 2. Stage 3 hypertension (high risk); 3. Type 2 diabetes.

Diagnosis and treatment

The patient experienced a focal neurological deficit, with the last episode occurring within 3 hours, meeting the criteria for intravenous thrombolysis [1]. After obtaining consent from the patient's family, 37.2 mg (0.6 mg/kg) of alteplase was administered intravenously for thrombolysis, with 3.72 mg given as a bolus within 1 minute, and the remaining 33.48 mg infused over 1 hour. Within 50 minutes post-thrombolysis, there was a noticeable improvement in left limb strength and speech, with the NIHSS score reduced to 1. At 24 hours post-thrombolysis, no significant abnormalities were observed on cranial CT. The patient started the following medications for secondary prevention and symptomatic treatment: oral aspirin 100 mg daily, clopidogrel 75 mg daily, atorvastatin 40 mg daily, propacetamol 0.5 g twice daily, cilostazol 10 mg once daily, and butylphthalide sodium chloride 25 mg injection twice daily. On August 9, 2022, the patient experienced recurrent episodes of right-sided weakness, aphasia, and facial asymmetry, totaling 5 episodes. After obtaining informed consent from the patient's family, tirofiban hydrochloride injection was continuously infused at a rate of 0.4 mg/kg/h for 24 hours, and the patient was sta-

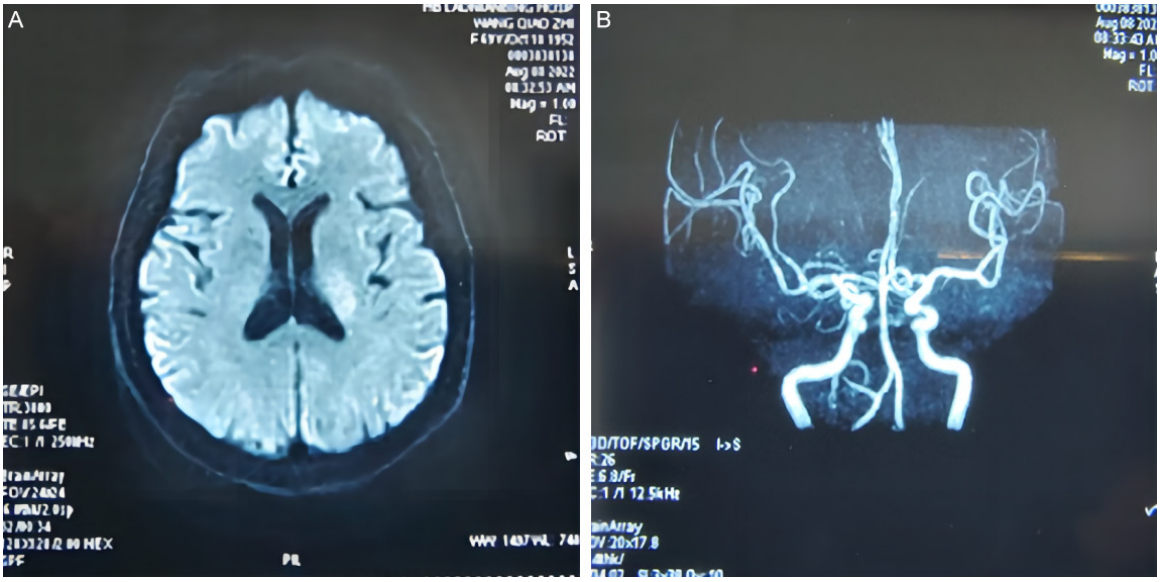

Figure 2. Head magnetic resonance imaging (MRI) examination. A: Head diffusion weighted imaging (DWI) shows acute cerebral infarction in the deep part of the left frontal lobe adjacent to the ventricle; B: Head magnetic resonance angiography (MRA) imaging is consistent with the imaging manifestations of atherosclerotic cerebrovascular disease.

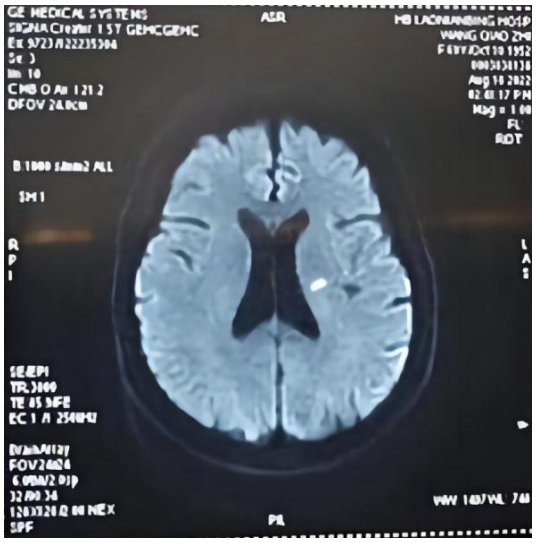

Figure 3. Left deep frontal lobe adjacent subacute cerebral infarction on diffusion weighted imaging (DWI).

bilized without further TIA episodes. Follow-up imaging on head DWI revealed subacute cerebral infarction adjacent to the left deep frontal ventricle (**Figure 3**), while neck MRA imaging showed no significant stenosis or occlusion of major blood vessels (**Figure 4**). On August 20, 2022, the patient exhibited grade 5 muscle strength in the right limb with an NIHSS score of 0. The patient was discharged with the following medications: oral aspirin 100 mg daily, atorvastatin 20 mg daily, and propacetamol 0.5 g twice daily. Follow-up assessments indicated stable condition with no further recurrence.

Discussion

Capsular warning syndrome (CWS) is a rare subtype of TIA, characterized by 3 or more episodes within 24 hours. It primarily manifests as unilateral limb motor and/or sensory abnormalities affecting two or more areas of the face, upper limbs, or lower limbs, without cortical involvement. Donnan first described CWS in 1993, with imaging showing infarctions typically in the internal capsule, thalamus, corona radiata, pallidum, putamen, corpus callosum, or brainstem [2]. While CWS accounts for only 1.5% of all TIA cases, the risk of progressing to irreversible neurological deficits within 7 days is 60% [2]. The exact pathogenesis remains unclear, but studies suggest an association with small artery perforating branch lesions [3], including inadequate perfusion in perforating branch supply areas, atherosclerotic plaque blockage at the origins of the perforating branches, or atherosclerotic narrowing of the perforating branches themselves.

In this case, the patient experienced left limb weakness, inability to speak, and facial asymmetry, with frequent episodes occurring within

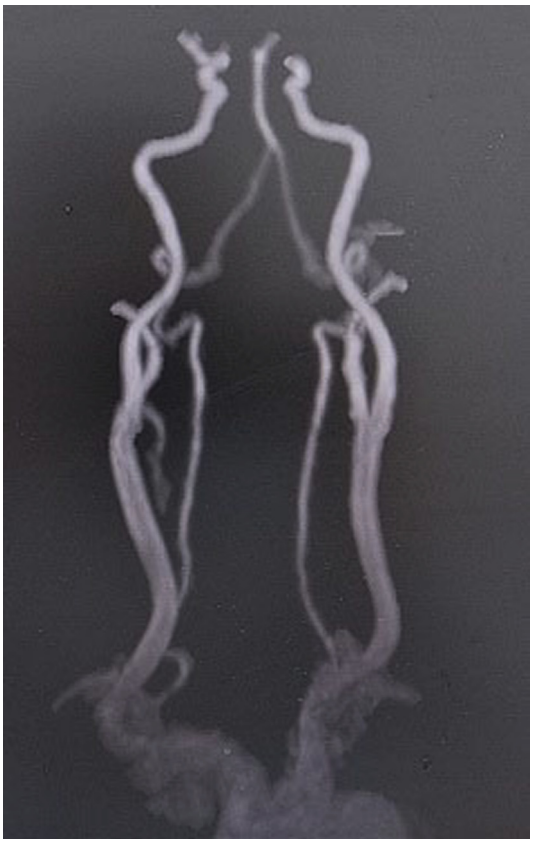

Figure 4. Neck magnetic resonance angiography (MRA) imaging shows no significant stenosis or occlusion of major blood vessels.

24 hours, totaling 7 instances. Notably, there were no signs of neglect or cortical deficits related to disuse. Head DWI revealed an acute cerebral infarction near the left deep frontal lobe, consistent with CWS diagnostic criteria. The patient had several atherosclerotic risk factors, including hypertension, type 2 diabetes, and multiple high-echo plaques in both carotid arteries as observed on neck artery color Doppler ultrasound. Additionally, head MRA imaging showed features consistent with atherosclerotic cerebrovascular disease. Excluding atrial fibrillation based on electrocardiogram and echocardiography, a clear diagnosis of intracranial and extracranial atherosclerosis was established. The patient's pathogenesis appeared to involve blockage of the perforating branch origin by atherosclerotic plaques from the middle cerebral artery, which increased the likelihood of occlusion in small brain vessels [4]. Studies by Sun Xu et al. [5] have shown that CWS patients exhibit narrowing of atherosclerotic brain vessels, with High-resolution magnetic resonance imaging (HR-MRI) showing unstable plaques of varying sizes, suggesting a strong correlation between CWS pathogenesis and perforating artery lesions caused by plaque instability.

Current treatment for CWS includes venous thrombolysis, antiplatelet therapy, anti-atherosclerosis treatment, anticoagulation, blood pressure management, or interventional therapy. Some cases have reported effective symptom control with high-dose antiplatelet and anticoagulant therapy, with venous thrombolysis being a widely used treatment for CWS [6]. In this case, despite receiving venous thrombolysis during the acute phase, the patient experienced five recurrent episodes within 24 hours. Continuous infusion of tirofiban hydrochloride sodium for 24 hours, followed by oral aspirin and clopidogrel 20 hours post-infusion, resulted in a favorable prognosis after one month of follow-up. This positive outcome was primarily attributed to the combined treatment with alteplase and tirofiban. Tirofiban is a reversible antagonist of fibrinogen binding to the GPIIb/IIIa receptor on platelets, inhibiting platelet aggregation in a dose- and solubility-dependent manner when administered intravenously. In some cases of perforating artery infarction, clinical features may fluctuate and progress, with poor response to venous thrombolysis, especially in CWS patients experiencing frequent recurrent symptoms. Studies [3, 7] have shown that intermittent tirofiban can reduce the frequency of CWS symptoms and shorten the duration of neurological deficits.

While some patients experience symptom recurrence despite antiplatelet therapy, intravenous thrombolysis within 4.5 hours of symptom onset remains safe and effective. In conclusion, CWS is characterized by frequent attacks and a high risk of infarction progression. Although there is no consensus on the optimal treatment for CWS, this case suggests that recombinant tissue-type plasminogen activator (r-tPA) combined with high-dose dual antiplatelet therapy is safe and effective for CWS patients with intracranial atherosclerotic stenosis (ICAS) [8].

Research [9] has demonstrated successful symptom control without severe bleeding complications following rt-PA thrombolysis in CWS patients resistant to conventional antiplatelet therapy. Recent investigation has identified several potential causes and pathogenic mech-

anisms of CWS, with HR-MRI emerging as a new diagnostic tool that highlights atherosclerotic plaques in intracranial arteries as a significant triggering factor. Additionally, combination therapy with venous thrombolysis, tirofiban, dual antiplatelet agents [9-11] has proven effective in suppressing disease progression and significantly improving patient outcomes. Given that CWS is associated with both intracranial and extracranial atherosclerosis, acute treatment with venous thrombolysis, followed by tirofiban within 24 hours, along with dual antiplatelet therapy and intensified lipid-lowering measures, can markedly improve patient prognosis. However, clinical trials remain limited, and broader randomized controlled trials are needed for further validation.

Conclusion

This study reports a case of CWS, in which the opening of the perforating branch was blocked by atherosclerotic plaques in the middle cerebral artery. The pathogenesis of CWS may be partially attributed to perforating artery lesions caused by vascular plaques. The combination of intravenous thrombolysis and tirofiban appears to significantly improve patient prognosis. However, further research, including randomized controlled trials, is necessary to validate this approach, though the rarity of such cases may pose challenges for large-scale studies.

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Disclosure of conflict of interest

None.

Address correspondence to: Yizhe Meng, Department of Neurology, Hebei Chest Hospital, No. 372 Shengli North Street, Shijiazhuang 050041, Hebei, China. E-mail: zhezhemeng2005@163.com

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