

rt-PA with Antithrombotic Therapies in a Case with Capsular Warning Syndrome

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Abstract

We herein report a case of capsular warning syndrome (CWS) that was successfully treated with recombinant tissue plasminogen activator (rt-PA). A 70-year-old woman had repeated stereotyped transient ischemic attacks (TIAs) of right hemiparesis and dysarthria. After hospitalization, argatroban, aspirin, and cilostazol were started but were ineffective. Thirteen hours after the first episode of TIAs, severe symptoms occurred. Magnetic resonance imaging showed acute infarctions in the internal capsule to corona radiata, so we used rt-PA. Since then, the TIAs have not occurred, and the symptoms have considerably improved. This case suggests that rt-PA might be effective and safe for use in treating CWS.

Key words: capsular warning syndrome, branch atheromatous disease, thrombolysis

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Introduction

Capsular warning syndrome (CWS) is a rare clinical syndrome first described by Donnan et al. (1) in patients who had recurrent stereotyped episodes of transient ischemic attacks (TIAs). Among all TIA patients, only 1.5% have CWS (2), and the prognosis of CWS is poor. About 40% to 60% of CWS patients develop a cerebral infarction within 10 days (1, 2). Many different treatments have been proposed, such as multi-target antiplatelet therapies (3-6), a loading dose of clopidogrel (4, 5), and recombinant tissue plasminogen activator (rt-PA) (7-15), but no effective therapy has yet been established. In addition, the efficacy of rt-PA on the outcome of CWS has not been determined.

Hemorrhaging is a typical complication of rt-PA for stroke patients but is rare for CWS (8, 14). We herein report a case of a CWS patient treated with rt-PA and antithrombotic therapies who had a good clinical course without any complications. In this case, rt-PA was effective and safe for a CWS patient.

Case Report

A 70-year-old woman with hypertension, dyslipidemia, and diabetes suddenly developed right hemiparesis and dysarthria at night. Her symptoms completely improved within 30 minutes, but because she had experienced the same episode 3 times, she was taken to our hospital. She had no history of drinking or smoking. Her blood pressure was 169/92 mmHg, there was no carotid bruit, and a neurological examination was normal when she arrived at our hospital. Within an hour of visiting our hospital, the same episode of transient right hemiparesis and dysarthria occurred twice.

The patient's complete blood cell and blood chemistry parameters were almost within normal limits. Carotid artery ultrasonography showed small isoechoic plaques on the right common carotid artery and left carotid bifurcation, and there was no obvious stenosis. Echocardiography and electrocardiogram revealed no abnormal findings. Magnetic resonance imaging (MRI) showed no acute cerebral infarctions. We diagnosed her with CWS, and she was hospitalized. We treated her with argatroban (60 mg/day), aspirin (100 mg/day), cilostazol (200 mg/day), atorvastatin (10 mg/day), and

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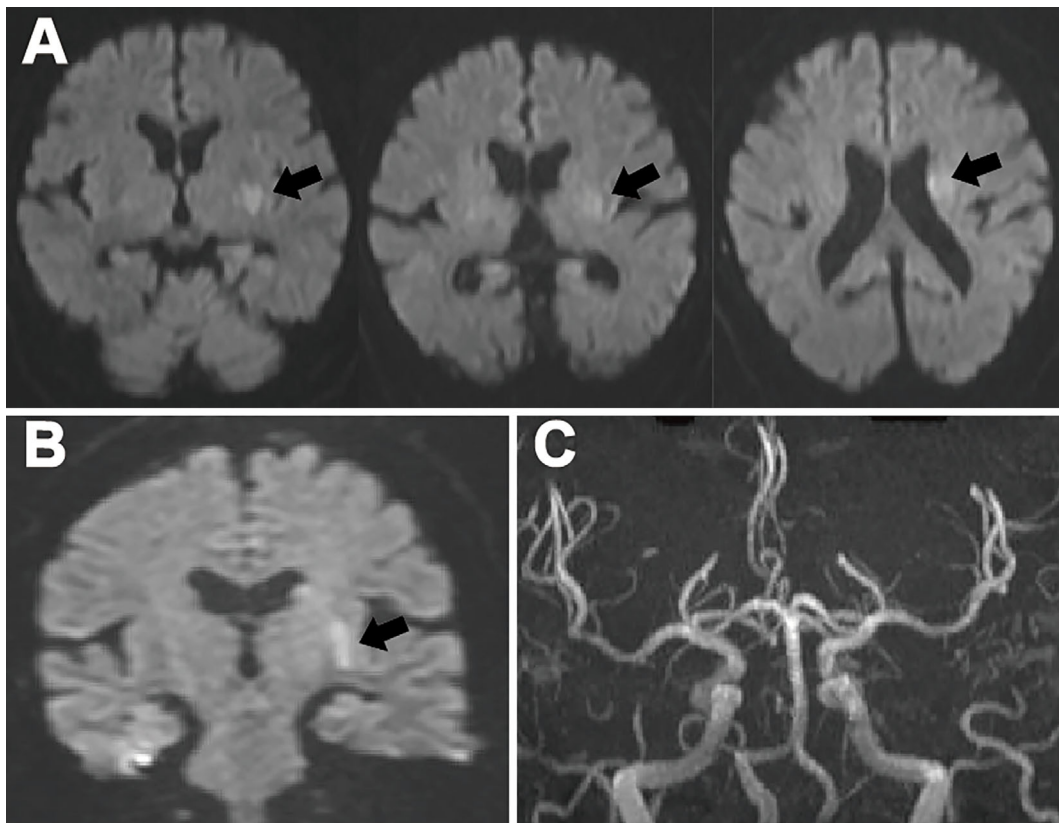


Figure 1. Brain magnetic resonance imaging (MRI) and MR angiography 13 h after the first episode of transient ischemic attacks. **A:** Diffusion-weighted imaging (DWI) axial view showing hyperintense areas in the left internal capsule to corona radiata (arrow). **B:** DWI coronal view showing hyperintense areas in the left internal capsule to corona radiata (arrow). **C:** MR angiography showing intact cerebral arteries.

edaravone (60 mg/day).

The treatments did not seem to be effective for her CWS in the acute phase. Thirteen hours after the first episode of TIAs, she developed more severe right hemiparesis and dysarthria, and her National Institute of Health Stroke Scale (NIHSS) score was 9 points. Diffusion-weighted imaging (DWI) on MRI showed slightly hyperintense areas in the left internal capsule to corona radiata (Fig. 1A, B), so we diagnosed her with acute cerebral infarctions. MR angiography did not detect any apparent stenosis of major cerebral arteries, including the left middle cerebral artery (Fig. 1C). We verified that there were no contraindications, obtained permission from the patient, and administered rt-PA 80 minutes after the most recent onset of neurological deficit. Her symptoms gradually improved, and her NIHSS score decreased to 3 points immediately after the end of rt-PA administration. TIAs have not occurred since then. The NIHSS score was 0 points 4 hours after the last onset of neurological deficit, although she still had slight right hemiparesis (Fig. 2). Over the course of administration, there were no marked changes in her blood pressure.

We verified that no bleeding was present using brain CT 24 hours after rt-PA administration and started argatroban, aspirin, and clopidogrel. The patient underwent rehabilitation, and her symptoms further improved, but she still had

very slight right hemiparesis, and her modified Rankin Scale score was 2 points. She was transferred to a rehabilitation hospital on the 29th day after her hospitalization.

Discussion

The term “capsular warning syndrome” was coined in 1993 to describe patients who have recurrent stereotyped episodes of motor or sensory deficits without cortical symptoms (1). A recent study showed that infarct locations of CWS vary; 50% of CWS patients have infarctions in the internal capsule, but the other half have infarctions in other locations (14). As such, some researchers and clinicians have suggested that the term “capsular warning syndrome” might not be adequate, and “vascular warning syndrome” or “stroke warning syndrome” has been used in some recent reports (8, 14, 15). Our patient had recurrent stereotyped episodes of TIAs, and MRI showed acute cerebral infarctions in the internal capsule to corona radiata, so we diagnosed her with CWS.

The pathophysiology of CWS has not yet been elucidated, but many hypotheses have been suggested, such as hemodynamic impairment owing to atherosclerotic severe stenosis of the proximal portions of the penetrating artery, microembolism from artery to artery or from the heart, vasospasm,

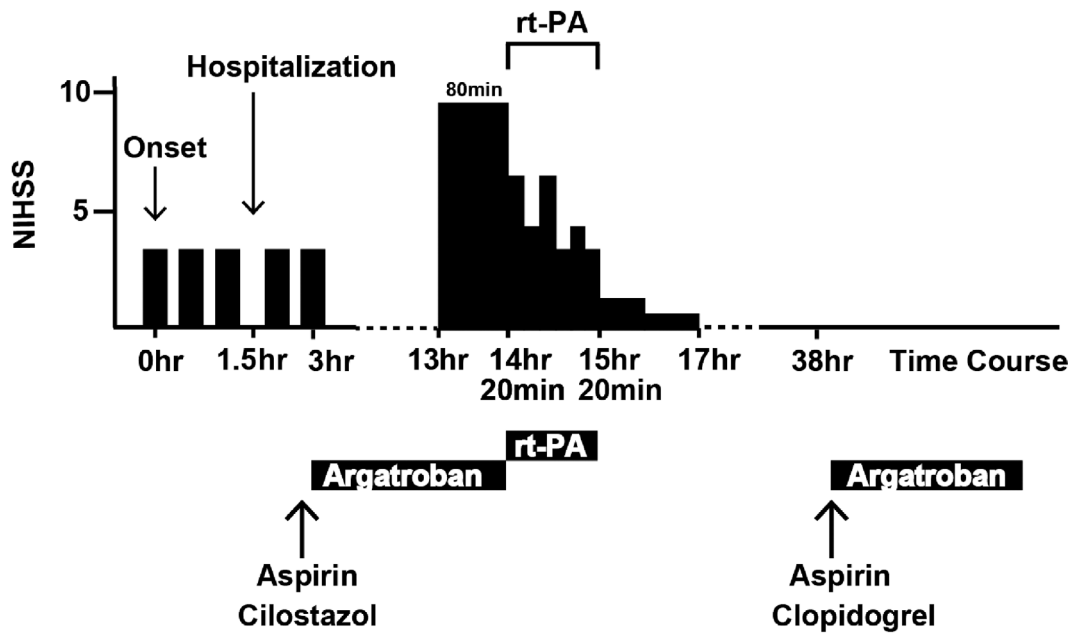


Figure 2. The clinical course of the patient. The horizontal bar shows the time course (hour); the vertical bar shows the National Institute of Health Stroke Scale (NIHSS) score.

or peri-infarct depolarizations (6, 16).

Our patient's infarctions were restricted to lenticulostriate arteries (LSAs) and were seated proximally along LSAs, so we concluded that this stroke type was branch atheromatous disease (BAD). BAD was first described in 1989 by Caplan (17) for an occlusion or stenosis at the origin of a deep penetrating artery of the brain leading to infarctions. The present patient had no obvious stenosis in the left middle cerebral artery, and we could not evaluate the LSAs by MR angiography. We speculate that there was atherosclerotic severe stenosis of the LSAs in the proximal position, which subsequently led to CWS and a BAD-type stroke.

No treatment for CWS has yet been established, and CWS patients have been treated in various ways. Classical therapy, including aspirin and heparin, is not sufficient (1, 16). In some reports, a loading dose of clopidogrel, with or without another antiplatelet therapy, is effective (4, 5). Intravenous thrombolysis therapy has also been used in some reports; Vivanco-Hidalgo et al. (11) reported that they treated four CWS patients with intravenous thrombolysis, and three of them made a full recovery, indicating that thrombolysis with rt-PA was effective for CWS. However, Tassi et al. (8) reported that rt-PA seemed to have lower efficacy than other therapies. Thus, the efficacy of intravenous thrombolysis is still controversial. Recent studies have reported that none of the CWS patients treated with rt-PA showed any symptomatic bleeding complications, suggesting that rt-PA might be safe for the acute phase of CWS (8, 14).

We initially treated our patient with argatroban, aspirin, cilostazol, atorvastatin, and edaravone without rt-PA because no symptoms were present and no acute infarctions were observed with MRI. However, these therapies were ineffec-

tive in the acute phase of CWS for the patient, and cerebral infarctions ultimately occurred. We immediately used rt-PA, which was very effective and had no complications. CWS has a high risk of developing cerebral infarctions, and when cerebral infarctions occurred in our patient, rt-PA was effective and safe.

As mentioned above, CWS is believed to be often caused by hemodynamic impairment due to atherosclerotic severe stenosis of the proximal portions of the penetrating artery. Typically, rt-PA is effective for fibrin clots. We therefore suggest that, in addition to atherosclerotic severe stenosis, unstable fibrin clots on the proximal portions of the penetrating artery may be involved in the pathophysiology of CWS, causing intermittent hypoperfusion and recurrent stereotyped TIAs.

Since 1993, many CWS cases have been reported, but the most effective therapy for CWS has not yet been determined. We herein reported a case of CWS that was successfully treated with rt-PA and other antithrombotic therapies. We found rt-PA to be effective without any complications. rt-PA may be an effective and safe treatment in CWS patients who develop cerebral infarctions.

The authors state that they have no Conflict of Interest (COI).

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