

# The Importance of Combined Antithrombotic Treatment for Capsular Warning Syndrome

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*Introduction:* Capsular warning syndrome (CWS) is characterized by recurrent conventional episodes of motor and/or sensory deficits without cortical symptoms. The purpose of this case series study was to evaluate the safety and appropriate treatment for CWS to prevent the development of complete stroke. *Methods:* We reviewed our hospital records and previous reports to find patients with neurologically fluctuating profiles, and excluded those with unknown details of initial treatment/final treatment of antiplatelet therapy or radiological findings. *Results:* We retrieved two cases of CWS from our hospital, which presented motor and/or sensory symptoms followed by complete resolution without complete ischemia. The recurring episodes in both were unable to be stabilized by single antiplatelet therapy but were successfully managed using two or more antiplatelet drugs. In 11 previously reported cases of CWS, the recurring episode was frequency stabilized with plural antiplatelet therapy. *Conclusion:* Multiplicate antiplatelet therapy is important for treatment of CWS, and caution is needed regarding hemorrhagic complications.

**Key Words:** Capsular warning syndrome—dual antiplatelet therapy—transient ischemic attack—hemodynamic infarction—lacunar symptoms

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## Introduction

Capsular warning syndrome (CWS) typically presents repetitive motor and/or sensory symptoms without cortical dysfunction, and was first described by Donnan in 1993.<sup>1</sup> It is important to elucidate the mechanism of CWS because the risk of established stroke in the first 7 days after CWS is 60%.<sup>2</sup> The etiology of CWS is believed to be related to atherosclerosis of the middle cerebral artery (MCA), but little is known about the exact pathological mechanism involved.<sup>3</sup> CWS is considered to be a distinct type of transient ischemic attack (TIA), but compared with TIA, the risk of developing complete stroke is particularly high in patients with CWS.<sup>4</sup>

Different treatment modalities have been proposed, including blood pressure therapy,<sup>5</sup> anticoagulation,<sup>1,4</sup> dual antiplatelet therapy,<sup>6,7</sup> and thrombolytic agents,<sup>8,9</sup> without conclusive data. To our knowledge, there is no established treatment for CWS. We here report two cases of typical CWS and compared them with previous cases. The purpose of this case series study was to evaluate the safety and appropriate treatment for CWS to prevent the development of complete stroke.

## Materials and Methods

We initially defined “capsular warning syndrome” as the clinical manifestation of acute neurological fluctuations in

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which symptoms improve until resolving completely or nearly completely, and reviewed published scientific reports by searching the PubMed database. The keywords used were “capsular warning syndrome,” “lacunar warning syndrome,” “acute stroke,” and “fluctuating stroke”. We reviewed related articles for all cases and excluded “pontine warning syndrome,”<sup>8,10</sup> and “callosal warning syndrome”<sup>11</sup> to clarify the therapeutic effects.

For all cases from our hospital records, we recorded the patient's sex, age, number of fluctuations, maximum score on the National Institutes of Health Stroke Scale (NIHSS), vascular risk factors—such as hypertension (HT), diabetes mellitus (DM), and dyslipidemia (DL)—radiological findings, and the content of acute treatment/secondary prevention. The same variables were collected from the previously reported cases if available (eg, initial treatment/final antiplatelet therapy and magnetic resonance angiography (MRA) findings).

## Results

We extracted 2 cases from our hospital (searching from January 2013 to December 2016) and 11 from the literature search (searching from 1990 to 2017 on PubMed searching). [Table 1](#) details the clinical presentation and outcomes for the 13 cases. The mean age was 57.9±13.1 years (range 31-72 years), and most of the patients were male (69.2%). Regarding symptoms, pure motor hemiparesis was common, the mean fluctuation frequency was 10.3 episodes (range 4-50 episodes), and the mean duration was 43.3 minutes (range 3-300 minutes). Among the risk factors, HT was the most common (69.2%), followed by DL and DM (23.0%). In this regard, vascular risk factors were similar with those for lacunar infarction. On MRA/CTA study, most patients did not have intracranial stenosis (84.6%). Of all cases, 38.4% were treated with single antiplatelet therapy and 53.8% were treated with anticoagulant/tPA for the initial treatment, but in 10/13 (76.9%), prevention of deterioration or recurrence was difficult. Therefore, dual/triple antiplatelet therapy was selected (clopidogrel 92.3% and aspirin 92.3% were used), and clinical symptoms resolved entirely. No hemorrhagic complications were observed for the cases from our hospital or in those from the literature search. In our TWO cases, blood pressure levels in the first 24 hours ranged above 150 mmHg (systolic). Below, we present our TWO cases in which control of recurrence on single antiplatelet therapy was difficult and fluctuation stabilized after dual antiplatelet therapy (DAPT) with eicosapentaenoic acid (EPA).

### Case 1

A 31-year-old man with HT, systolic blood pressure that was well-controlled at 120 mmHg, and DL treated with rosuvastatin, exhibited an episode of dysarthria

lasting 20 minutes. Cerebral MRI demonstrated no significant abnormalities and the symptom completely recovered quickly. Two subsequent recurrences (dysarthria and left-hand clumsiness) lasting 10-20 minutes occurred within 10 days. He was evaluated at the emergency department and MRI revealed acute ischemic lesion at the right internal capsule, but neurological findings were unremarkable. There was no significant stenosis on MRA and cervical echography, no arrhythmia, including paroxysmal arterial fibrillation, on Holter electrocardiogram (ECG), and no remarkable abnormalities on transesophageal echocardiography (TEE). Antithrombotic therapy (aspirin and argatroban, which is an intravenous anticoagulation drug that directly inhibits thrombin<sup>12</sup>) and edaravone were started and were then switched to clopidogrel (75 mg daily). He was discharged without recurrence but developed dysarthria lasting 100 minutes again at 23 days after discharge. MRI demonstrated acute infarction at the same lesion ([Fig. 1](#)). As antithrombotic therapy, an additional 75 mg of clopidogrel and 200 mg of aspirin and argatroban were administered immediately. Calcification from the right top of the internal carotid artery to the MCA was noted on 3D-CT angiography. During hospitalization, he exhibited frequent episodes of dysarthria lasting 20 minutes. He was then started on DAPT with 75 mg of clopidogrel and 200 mg of cilostazol. If no attacks were observed during the 1-month follow-up, we planned to change back to single cilostazol therapy. However, frequent episodes of dysarthria lasting several minutes occurred, and DAPT (clopidogrel and cilostazol) was restarted. On DAPT, he developed perioral numbness for several minutes without dysarthria. DWI changes on MRI. Therefore, we added 1800 mg of EPA based on the results of the JELIS trial<sup>13</sup> and strictly controlled for vascular risk factors. After starting EPA treatment, no neurological changes were observed.

### Case 2

A 62-year-old man with a history of lacunar stroke on the left internal capsule 5 years before admission was treated with 100 mg of aspirin as secondary prevention. Three years after the initial attack, he experienced two episodes of recurrence in the same lesion and was switched to 75 mg of clopidogrel. However, left hemiparesis and dysarthria reappeared, and he was admitted to our hospital. Brain MRI demonstrated acute ischemia in the left internal capsule ([Fig. 2](#)). His NIHSS score evaluated in the emergency room was 4 points, but his symptoms immediately improved after MRI. Laboratory data and ECG were unremarkable. There were no significant findings on TEE and no pulmonary arteriovenous fistula on CT-angiography. After admission, frequent recurring episodes occurred, and he was administered DAPT (75 mg of clopidogrel and 100 mg of aspirin). However, even on DAPT,

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