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Capsular warning syndrome and resistance to dual antiplatelet therapy: A clinical dilemma

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ABSTRACT

Background. Capsular Warning Syndrome (CWS) involves multiple stereotypical transient ischemic attacks (TIAs) within 24 hours, often preceding a more severe ischemic stroke. This serves as a critical warning sign, emphasizing the need for urgent medical intervention.

Case report. We report a 65-year-old diabetic and hypertensive woman who experienced transient recurrent episodes of mouth deviation and slurred speech, lasting 10 seconds each, with full recovery. Initial MRI showed no abnormalities, and she was started on dual anti-platelets. Despite treatment, she developed sudden right-sided hemiplegia, with MRI showing a hyperacute non-hemorrhagic infarct in the left ganglio-capsular region. She was treated with intravenous Tenecteplase, resulting in significant neurological recovery.

Conclusion. This case highlights the importance of early identification of CWS. Despite dual antiplatelet therapy, CWS can progress to ischemic stroke, posing a treatment challenge. Further research is needed to establish optimal treatment protocols for CWS.

Keywords: acute CVA, brain infarct, transient ischemic attacks, ischemic stroke, stroke, capsular warning syndrome

Abbreviations:

CWS: Capsular Warning Syndrome

TIA: Transient Ischemic Attack

CT: Computed Tomography

MRI: Magnetic Resonance Imaging
NIHSS: National Institute of Health Stroke Score
mRS: Modified Rankin's Score
ASA: American Stroke Association.

INTRODUCTION

Capsular Warning Syndrome (CWS) is defined as the occurrence of at least three stereotypical episodes of transient ischemic attacks (TIAs) within a short time frame, usually 24 hours, with complete recovery between episodes and no cortical symptoms [1]. The clinical presentation often involves motor or sensory deficits that are transient but repetitive, indicating a high risk of an impending stroke [2]. This pattern of repeated TIAs serves as a critical warning sign, emphasizing the need for urgent medical intervention to prevent a more severe and potentially disabling ischemic event [3,4]. The incidence of CWS among patients presenting with recurrent TIAs is relatively low, estimated at 1.5-4.5%, but the risk of progression to stroke within seven days can be as high as 60% [5]. Recent studies have highlighted the role of neuroimaging, particularly MRI with diffusion-weighted imaging (DWI), in identifying patients at high risk for stroke and guiding treatment strategies [6]. However, despite advances in imaging and treatment, there remains variability in outcomes, underscoring the need for further research to optimize care for these patients [7].

CASE REPORT

A 65-year-old woman with a history of Type 2 Diabetes Mellitus and Systemic Hypertension, who is a non-smoker, presented to the outpatient department with complaints of two brief episodes of deviation of the angle of the mouth to the left earlier that morning. Each episode lasted about 10 seconds and was associated with slurred speech. Both episodes resolved spontaneously without any residual symptoms. The patient had no prior history of similar episodes, stroke, or heart disease. On examination, her vital signs were stable, and a neurological assessment revealed no focal deficits. An initial MRI of the brain showed no signs of infarction or hemorrhage. After being admitted to the hospital, the patient experienced two additional episodes with similar symptoms, again without any lasting deficits. She was immediately started on dual anti-platelets and statins. All four transient episodes occurred within a 12-hour period.

Following these episodes, the patient suddenly developed weakness in the right upper and lower limbs, accompanied by a deviation of the angle of the mouth to the left.

Neurological examination revealed decreased muscle tone in the right upper and lower limbs, a muscle power grade of 0/5 in right upper and lower limbs, diminished deep tendon reflexes on the right side, and an extensor plantar reflex on the right. A cranial nerve examination indicated a right upper motor neuron (UMN) facial palsy. A repeat MRI of the brain revealed a hyperacute non-hemorrhagic infarct in the left ganglio-capsular region. (Figure 1)

Thrombolytic therapy was administered immediately as an intravenous bolus of Tenecteplase in the dose 0.25 mg/kg. The patient showed significant improvement in motor function within two hours, with only minimal residual weakness. A follow-up CT scan of the brain performed 24 hours later showed no evidence of haemorrhage. NIH Stroke Score improved from 13 at onset to 3 at 24 hours.

Further work-up, including carotid Doppler, echocardiogram, and 24-hour Holter monitor, was normal. She was started on a neuro-rehabilitation program, and her Modified Rankin Scale (mRS) score improved from 4 at onset to 0 at six-month follow-up, indicating no residual disability.

DISCUSSION

Capsular Warning Syndrome (CWS) was first described in 1993 by Donnan et al as a distinct clinical syndrome characterized by recurrent, stereotypical episodes of transient ischemic attacks (TIAs) that primarily involve motor or sensory deficits [1]. These episodes, which usually affect one side of the body, occur over a short period and are attributed to transient ischemia in the small penetrating arteries supplying the internal capsule. Donnan noted that CWS frequently precedes a lacunar stroke and proposed that these recurrent episodes act as a warning sign for an imminent, more significant ischemic event, thereby coining the term "Capsular Warning Syndrome"[1].

Since its initial identification, further studies have broadened our understanding of CWS, recognizing it as a type of "crescendo TIA" syndrome [7]. The neurological deficits typically associated with CWS include pure motor hemiparesis or sensorimotor deficits, which tend to resolve spontaneously, as observed in our patient.

Advanced neuroimaging, particularly MRI with diffusion-weighted imaging (DWI), plays a critical role in detecting small, hyperacute ischemic lesions that may not be visible on standard MRI or CT scans. Ay et al demonstrated that DWI could identify early ischemic changes in the internal capsule even when conventional imaging appears normal, thereby facilitating the early diagnosis of CWS [8].

The management of Capsular Warning Syndrome aims to prevent progression to a full-blown stroke, given the high risk associated with recurrent TIAs. Immediate medical

intervention typically includes the use of antiplatelet agents, such as aspirin or clopidogrel, to reduce the risk of thrombus formation in small, penetrating arteries [9,10]. In cases where stroke does occur, intravenous thrombolysis may be administered according to guidelines set forth by the American Heart Association (AHA) and the American Stroke Association (ASA) [11]. This has been supported by various case reports [12-14]. Supportive treatments also encompass strict control of blood pressure, optimization of blood glucose levels in diabetic patients, and appropriate lipid management to mitigate any underlying stroke risk factors [15]. Aggressive management of these factors is essential for stabilizing the patient and preventing further ischemic events.

Fahey et al mention a case of Capsular warning syndrome which was resistant to aspirin and a loading dose of clopidogrel was tried [16]. Another article by Vivek Nadarajan et al describes a case of dual anti-platelet resistant capsular warning syndrome, and the challenges in treatment [17]. This was indeed the case in our patient, who developed ischemic stroke in spite of treatment with dual anti-platelets and statins. Thrombolysis was performed, which led to a significant improvement in the outcome, and should be considered when patient shows signs of anti-platelet resistance.

CONCLUSION

This case highlights the importance of recognizing Capsular Warning Syndrome (CWS) as a critical neurological condition that can precede a significant ischemic stroke. Despite dual antiplatelet therapy, CWS can progress to ischemic stroke, posing a treatment challenge. Thrombolysis may provide a valuable option in such cases, as demonstrated in our patient, who had a favorable outcome following Tenecteplase administration. Further research is needed to establish optimal treatment protocols for CWS.

Patient consent:

We hereby certify that we have obtained written informed consent from the identified individual for the presentation of their case within the scientific paper titled 'Capsular Warning Syndrome and Dual Antiplatelet Resistance: A Clinical Dilemma.' Every effort has been made to protect the patient's anonymity. Identifiable information, including personal details, has been omitted or anonymized to prevent identification. However, due to the specificity of the case, there remains a possibility that individuals familiar with the patient may be able to identify them.

Conflict of interest:

We, the authors, declare that this manuscript is original, has not been published elsewhere, and is not under consideration for publication elsewhere. We declare no competing interests related to this article. No financial assistance has been received for this case report. We certify that we do not have any financial or personal relationships that may bias the content of this work.

Authors' contributions:

- **Conceptualization:** Sornavalli Valliappan, Mariraj Indiran, Ponambalaganapthi Nadar, Vivekanandan Thiyagarajan, Fahad Dadu
- **Design:** Sornavalli Valliappan
- **Data Curation:** Sornavalli Valliappan
- **Writing – original draft:** Sornavalli Valliappan
- **Writing – Review and Editing:** Sornavalli Valliappan, Mariraj Indiran, Ponambalaganapthi Nadar, Vivekanandan Thiyagarajan, Fahad Dadu
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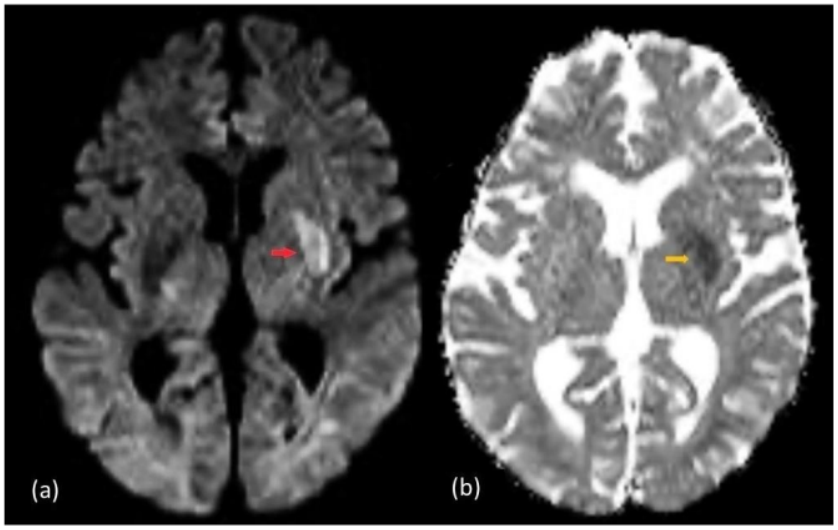
FIGURES

Figure 1: MRI brain - Diffusion Weighted Imaging (DWI)



(a) Shows diffusion restriction in the left corona radiata and ganglio-capsular region (red arrow).

(b) Corresponding Apparent Diffusion Co-efficient (ADC) shows a hypointense signal in the same region (yellow arrow), without any SWI blooming, indicating a non-hemorrhagic hyperacute infarct.