Capsular Warning Syndrome - A Case Series and Discussion on Management Dilemmas

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Abstract

Background: The term ‘Capsular warning syndrome (CWS)’ refers to recurrent, stereotypical transient ischemic attacks, either motor, sensory or both, without cortical symptoms or signs. Of these patients, 42-71% go on to develop infarcts. There are no defined treatment guidelines for this lesser known entity.

Methods: We studied 9 patients who presented over last 2 years to our hospital with recurrent and stereotypical transient ischemic attacks suggestive of capsular warning syndrome. Their clinical characteristics, neuroimaging findings, relevant etiological investigations, management and outcomes were studied.

Results: Seven out of 9 patients were under 40 years of age. The commonest presentation in our series was a pure motor syndrome. The duration of neurologic deficits ranged from 5 minutes to 20 minutes with complete recovery in between episodes. Three patients had concordant abnormalities on CT brain angiography. Five out of 9 patients received IV thrombolysis with t-PA. One patient worsened neurologically post thrombolysis, whilst the others improved clinically.

Discussion: Despite multiple hypotheses, the pathogenesis and management of CWS has not been established clearly. Due to fluctuating neurological symptoms with complete recovery in between the episodes, there is a dilemma concerning treatment of such patients with intravenous thrombolysis. However, intravenous thrombolysis appears to be safe in CWS as in acute ischemic stroke, followed by treatment with antiplatelet agents.

Introduction

The Capsular warning syndrome (CWS) is defined as the occurrence of at least three recurrent stereotypical transient ischemic attacks in 24 hours, being purely motor, sensory or both, involving 2 of the 3 regions of face, arm and leg.1 No cortical symptoms or signs should be present. Among these patients, 42-71% go on to develop a capsular infarct.1,2 The pathogenesis of this syndrome is largely hypothetical, with mention of hemodynamic impairment, vasospasm, artery-to-artery embolism, peri-infarct depolarization, and cardio-embolic source as putative etiologies.1,2 Hence, optimal treatment in acute stage as well as for further prevention of strokes, is controversial. Herein, we report our experience of 9 cases of CWS and discuss the management conundrum.

Patients and Methods

We describe 9 cases that fulfilled the definition of CWS that were treated at our centre in the past 2 years (Table 1). CT brain and CT angiography were done at time of presentation to look for intracranial bleed and occlusion of a large vessel whilst MRI brain was done 24 to 48 hours later for most of the patients. To determine the etiology, patients underwent further investigations like 2D Echo, thrombophilia profile, sickling test, etc. Seven patients were treated with intravenous thrombolysis with tPA. This was followed by treatment with dual antiplatelet agents starting 24 hours post thrombolysis, after ruling out intracerebral hemorrhage on repeat CT brain. Written informed consent was obtained from all patients/relatives for data collection and publication.

Case 1

A 38 year old male was brought at 12 noon to Emergency room with a 3 hour history of right hemiparesis. He had no prior TIAs, HT, DM or cardiac history, was not a substance abuser, and was on no medications. His BP in left UL was 120/88 mm Hg, and he had a regular pulse rate of 110/m. He was alert, fully oriented, dysarthric due to right UMN facial weakness, and had Rt hemiparesis of Gd 0. His NIHSS was 14 at 3 hrs 15 min after onset of symptoms. CT brain and angiography were normal and ASPECTS score was 10. He was thrombolysed at 12.54 pm with IV tissue plasminogen activator (tPA). Within 20 minutes, his power improved to Gd 4, and facial weakness resolved. However, in the next 20 minutes, power fluctuated twice from Gd 4 to 0 and back again to Gd 4. We repeated a CT brain and Angiogram, and performed a 2D Echo, all of which were normal. At 1 hour post- thrombolysis, power was Gd 0 on the hemiparetic side.

MRI done at that point showed a left gangliocapsular infarct (DWI-ADC concordant), with FLAIR images already showing concordant signal abnormalities (Figure 1). No bleeding was seen.

Patient had a complete hemorheological investigation including sickling test, thrombophilia workup, and homocysteine level, and had a bubble Echo study performed, all of which were normal. He made a complete recovery over 2 weeks and was discharged on double antiplatelets with statins.

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Table 1: Clinical and Imaging features, treatment and in-hospital outcome in 9 patients with Capsular Warning Syndrome

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Sex</th>
<th>Time to Presentation after last episode (hrs)</th>
<th>Deficit</th>
<th>NIHSS</th>
<th>No. of Fluctuations/Time Period hours</th>
<th>CT Brain</th>
<th>CT/MR Angio</th>
<th>MRI</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38/M</td>
<td>3</td>
<td>Rt hemiparesis</td>
<td>14</td>
<td>3/4.5</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Left GC* infarct</td>
<td>IV thrombolysis at 4 hours</td>
</tr>
<tr>
<td>2</td>
<td>18/F</td>
<td>2.5</td>
<td>Lt Hemiparesis</td>
<td>8</td>
<td>15/48</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>R Post IC** infarct</td>
<td>IV thrombolysis at 3 hrs</td>
</tr>
<tr>
<td>3</td>
<td>13/M</td>
<td>8</td>
<td>Rt Hemiparesis</td>
<td>2</td>
<td>6/128</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>L CS* post IC</td>
<td>Standard</td>
</tr>
<tr>
<td>4</td>
<td>21/F</td>
<td>24</td>
<td>LtFaciobrachial</td>
<td>0</td>
<td>2/8, 6 mths ago- 22/72</td>
<td>N Abnormal</td>
<td>N</td>
<td>N</td>
<td>Standard</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>17/F</td>
<td>Not acute</td>
<td>Rt Hemiparesis</td>
<td>0</td>
<td>2/3, 1 mth ago-2/4</td>
<td>Left M2 narrow</td>
<td>MR</td>
<td>N</td>
<td>Standard</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>50/M</td>
<td>Ongoing</td>
<td>Rt Hemiparesis</td>
<td>11</td>
<td>5/12</td>
<td>N initially, Rt GC N infarct on repeat</td>
<td>Not done</td>
<td>MRI</td>
<td>IV thrombolysis 1 hr after onset</td>
<td>Recovered</td>
</tr>
<tr>
<td>7</td>
<td>30/M</td>
<td>Ongoing</td>
<td>Rt Hemiparesis</td>
<td>0-6</td>
<td>3/3, 4/24, a week ago</td>
<td>Left SC** infarct</td>
<td>Left IC complete block</td>
<td>Not done</td>
<td>MRI</td>
<td>Thrombolysed 1 hour after episode</td>
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<tr>
<td>8</td>
<td>64/M</td>
<td>Ongoing</td>
<td>RtHemiparesis</td>
<td>7-8</td>
<td>8/14</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>L GC infarct 6 days later</td>
<td>Heparin Aspirin</td>
</tr>
<tr>
<td>9</td>
<td>28/M</td>
<td>4 hrs</td>
<td>RtFaciobrachial</td>
<td>3</td>
<td>4/7 hrs</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>L IC acute infarct</td>
<td>IV thrombolysis</td>
</tr>
</tbody>
</table>

Key: *- Gangliocapsular; **- Internal Capsule; ≠- Centrum Semiovale; Ω- Corona Radiata; ∑- Striatocapsular

Case 2

An 18 year old girl was brought with recurrent left hemiparesis, totalling 14-15 episodes over 2 days, each episode lasting 5-8 mins. She had had no recent viral exanthematous fevers or vaccinations. At presentation to us, she had Left hemiparesis of 3/5 power with a left UMN facial weakness, NIHSS score being 8. Her vital parameters were normal, including cardiac examination and carotid pulsations.

ASPECTS score was 10 on CT brain with a normal angiography. She recovered to normal power in 20 mins. She was thrombolysed with tPA at 3 hours after her last episode. Repeat CT at 24 hours, and Echocardiogram were normal.

MRI showed diffusion restriction with concordance on ADC, in right posterior limb of internal capsule (Figure 2).

All hemorheological, and structural causes were ruled out on investigation. She continued to be asymptomatic over the next 3 weeks, on antiplatelets and statins.
Case 3

A 13 year old boy presented to us with 5 episodes 5 days ago, and 1 episode on day of presentation, comprising headache, body pain progressing to Right hemiparesis, and slurred speech lasting 5 minutes each time. He had no past history of migraine or seizures, and had had no recent vaccinations or exanthematous fevers. His blood pressure was 100/70 mm Hg and pulse was regular at 80/m. He had a widely split S2.

Possible diagnoses considered were CWS, hemiplegic migraine, or seizures with Todd’s palsy. While his CT brain and Angiography were normal, MRI showed an acute infarct in left Centrum semiovale and posterior limb of Internal capsule (Figure 3). He was managed conservatively with antiplatelets, and continued to have 1 daily episode of weakness lasting a few minutes, while in the ward. He was detected to have a Bicuspid Aortic valve with commissures at 10 and 4 O’clock positions. Thrombophilia workup showed no abnormality.

Case 4

A 20 year old woman presented with 2 episodes of left faciobrachial weakness, lasting 6-8 minutes, over 8hours. Six months before this presentation, she had had 15-20 similar episodes of left faciobrachial weakness, Gd 0-2, lasting 5-8 mins, over a period of 3 days. She had taken treatment at that time, but had not continued any medications. Clinically, her vital parameters and neurological examination were normal, except for mild torticollis to the right.

Her CT and MRI brain were normal. MR angiography showed long-segment narrowing of left vertebral artery, narrowing of left internal carotid in cavernous portion, and absence of left A1 segment of ACA. MRI brain stroke protocol was normal.

Case 5

A 17 year old girl presented with 2 episodes of left Hemiparesis without facial involvement, in Jan 2020, lasting 6 minutes each, over 3 hours. She had had
2 prior episodes in the previous month, each lasting 5-15 minutes, over 4 hours. She had had no recent vaccinations or exanthems.

At presentation, she was on Aspirin 150 mg daily for the previous 2 wks. All investigations, including sickle testing, bubble echo, Lipoprotein levels, and thrombophilia workup, were normal. MRI done the previous month had shown an acute infarct in deep white matter on the right side, with some restricted diffusion in right frontal cortex, and a possible M2 narrowing (Figure 5). However, at present episode, CT brain and angiography and MRI were normal.

She had a history of migraine without aura, of 2-3 years duration. A combination of Aspirin and Clopidogrel was started, and Flunarizine was added. She continued to be asymptomatic over the next 3 months.

**Case 6**

A 50 yr old man presented with a flurry of 5 episodes of left sided hemiparesis with UMN facial weakness over the past 12 hours. During presentation, he had an NIHSS score of 11, but the deficit recovered fully within 10 minutes. CT brain and CT angiography were normal, and the patient was thrombolysed with tPA at 1 hour post the last episode. He remained asymptomatic till discharge 4 days later. Repeat CT at 24 hours post thrombolysis showed a gangliocapsular infarct on the right side (Figure 6).

**Case 7**

A 30 yr old male, newly detected to have hypertension, presented with 3 TIAs over 3 hours, each lasting 5-10 mins. He had had a similar episode a week ago. The deficit included a right hemiparesis with facial weakness. At presentation, his NIHSS fluctuated from 0-6. His ECG showed inferolateral
A 28 year old man presented with recurrent right faciobrachial weakness, having had 4 episodes over 7 hours, lasting 5-7 minutes each time. His NIHSS was 3 during 1 such episode in the emergency room. CT brain and CT angiography were normal. His Hb was 17 gm %, with no clinical signs of dehydration. He was thrombolysed at 4 hours after the last episode. The decision to thrombolysé despite low NIHSS was taken in view of dominant upper limb being involved, and young age of patient. MRI brain done at 14 hours after thrombolysis showed a left Internal Capsule acute infarct (Figure 9). He had recovered partially at discharge, with no further episodes.

**Discussion**

Pathogenesis, and hence, management of CWS are debatable. It has been proposed that even as early as 48 hrs post-stroke, patients with subcortical infarction engage bilateral prefrontal, ipsilateral posterior parietal and bilateral sensorimotor cortices during a finger-sequencing task. The fluctuations that are observed in CWS may represent perturbation of this complex network, in some patients. However, it is surprising that fluctuations persist, even after infarction has occurred, as seen in our patients.

There are anecdotal reports of focal arterial pathology causing CWS. It has been proposed that when there is a single dominant Lenticulostriate artery supplying the deep motor tracts, instead of multiple small penetrating vessels, then a proximal MCA stenosis can result in this syndrome. Additionally, atherosclerotic plaques on the ventral wall of MCA at the origin of the lenticulostriate arteries, demonstrated by high resolution MRI, have been proposed as the causation of CWS. There has also been an anecdotal report of Anterior choroidal artery stenosis causing CWS.

In our series, 7/9 patients were under 40 years of age, a finding which is different from other larger series (In Paul et al’s series, the mean age was 73 years). The presence of this fluctuating vascular subcortical syndrome in the young, throws up the possibility of an immature supplementary network that fails to function during the episodes.

Since the majority of our patients were young, without traditional vascular risk factors, it was important to investigate fully for a cause, despite the infarcts being subcortical. Cerebral CT angiography, 2D Echocardiogram (Transthoracic Echocardiography may be required), cardiac rhythm recording, and hemorrhheology would be mandatory in younger patients. Among our 9 patients, 3 had definite concordant angiographic abnormalities on CT angiography. Patient no. 5 had been documented to have a concordant M2 narrowing at a previous episode. She also had a history of migraine, and had had the present episode while on Aspirin. It was possible that migraine induced vasospasm, or Reversible vasoconstriction syndrome was the cause of her deficit, although CT angiography at the present episode was normal. Flunarizine was added to the Aspirin- Clopidogrel combination at the present episode for this patient.

All except one patient had a normal Echocardiogram, the single exception being patient 3, who had a bicuspid aortic valve, with no arrhythmia.

The commonest presentation in our series was a pure motor syndrome, which was consistent with the reports by He et al and Hawkes et al. An infarct was almost always seen on CT/MRI in our patients in the first few hours after presentation (even while the patient was fluctuating clinically), or on a repeat CT at 24 hours, but the patients continued to do well clinically. Site of infarct was distributed between Striatocapsular area, posterior limb of Internal capsule, Corona radiata and Centrum semiovale in our patients. In He et al’s series, internal capsule was the commonest area of involvement.

Treatment of this syndrome is controversial. There are anecdotal reports of successful stenting of the proximal arterial stenosis with a good outcome. However, this pathology is rarely demonstrated, and in the majority of cases, the question is whether to thrombolysé or not, in the fluctuating scenario. Tassi et al, in a retrospective analysis of ischemic strokes over a 5 year period, found that 18/967 patients had a “Stroke warning syndrome”, and that 9 of them received IV tPA, with a good outcome in one third of these patients at 3 months; however, 55% in the ‘no tPA group’ of this subset also had a good outcome. Another group has reported a short case series of 4 patients with CWS who received IV tPA within 4 hours of onset, with ¼ patients
showing complete clinical recovery, and a normal MRI, at 1 week. Overall, IV thrombolysis appears to be as safe in CWS as in general acute ischemic stroke. Intravenous thrombolysis was done in 5/9 patients in our series, with excellent clinical outcome in most patients. In case 7, thrombolysis was done despite CT showing an infarct, as the patient was clinically fluctuating, the infarct appeared to be evolving, and there was a concordant large artery thrombosis. In fact, a conventional angiography was planned to be done at the earliest for this patient for any further intervention, but he worsened rapidly and was discharged against medical advice. It is possible that his worsening may have been part of the ongoing fluctuations, with later improvement. Among the patients who were not thrombolysed, one patient was seen a few months after the episodes and was doing well on Aspirin, while another refused thrombolysis but was stable on Aspirin; the third patient, as mentioned above, was treated for possible migraine induced vasospasm and continued to do well.

Various case reports have mentioned efficacy of individual or combinations of antiplatelet agents in the treatment of CWS. Fahey et al found a loading dose of Clopidogrel to be efficacious in 2 patients who were 'Aspirin resistant'. Kawano et al, and Asil et al, in separate case reports, also reported combination antiplatelet agents to be of benefit. Jiao et al reported favorable outcome in a patient with stuttering lacunar syndrome. Fahey et al, and Asil et al, in separate multicentre analysis by He, Xu et al, analysing treatment effects in CWS, the difference in therapeutic effects between the rt-PA, single and double antiplatelet groups was not statistically significant. Our patients are on single or double antiplatelets and statins, with a plan to modify treatment after 3 months.

In conclusion, the pathogenesis of CWS continues to be debated. It is essential to look for any underlying angiographic, cardiac or hemorrhological factors, especially in younger patients with no vascular risk factors. Intravenous thrombolysis is safe and should be done early, despite ongoing clinical fluctuations, to prevent a resultant disabling stroke.

References