

# Capsular Warning Syndrome: Report of A Case

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**Abstract-** The “capsular warning syndrome” (CWS) is characterized by recurrent stereotypical episodes of motor and/or sensory dysfunction without cortical signs. CWS is a clinically well recognized entity, and carries a significant risk of capsular infarct. The ischemia is most likely ascribable to hemodynamic changes in diseased small penetrating vessels. Treatment remains controversial and none has been proven effective. We described a 66-year-old man having 15 episodes of stereotypical transient ischemic attack within four days. The findings of the diffusion-weighted image showed abnormalities confined concurrently to the left lateral thalamus, posterior globus pallidus, and posterior corona radiata while the internal capsule was spared. These findings suggest involvement of the territory of anterior choroidal artery. We also documented changes in the pattern of attacks after initiation of intravenous urokinase.

**Key Words:** Capsular warning syndrome, Urokinase, Transient ischemic attack, Anterior choroidal artery

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## INTRODUCTION

G. A. Donnan and colleagues first described a form of transient ischemic attack (TIA) presenting as crescendo episodes of ischemia functionally localized to the internal capsule<sup>(1)</sup>. This is called “capsular warning syndrome” (CWS) because around 40% of these cases finally developed dense hemiplegia. The final infarct of most CWS patients involved a single penetrating artery, although infarctions involving striatocapsular or anterior choroidal arteries occasionally occurred<sup>(2)</sup>. Typically, these patients are refractory to conventional therapies including hemodilution, anticoagulation, or thrombolysis. We described a case of ischemic stroke with proba-

ble involvement of the left anterior choroidal artery and having frequent episodes of right hemiplegia without signs of cortical dysfunction. The pattern of attacks changed after the use of intravenous urokinase.

## CASE REPORT

A 66-year-old man with a history of untreated hypertension developed sudden-onset dizziness on his way to the toilet before sleep at 10 pm on July 17, 2006. Within seconds to minutes, he started to have slurred speech and weakness in the right limbs. He did not have double vision, vertigo, nausea, headache, numbness, or dysphagia. Also, there was no prior history of stroke,

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migraine, arrhythmia, diabetes mellitus, or other cardiac diseases. He was escorted to the emergency department at 10:29 pm. On arrival, the blood pressure was 167/89 mmHg. He was found to have dense right hemiplegia and the National Institute of Health Stroke Scale (NIHSS) was 11. The findings of the brain computed tomographic examination done at 11 pm. were within normal limits. His condition fulfilled the criteria for tissue-plasminogen activator (tPA) therapy. Despite the informed consent from the family, tPA therapy was not performed because the patient's muscle power improved markedly (to 4/5) at midnight. Intra-venous infusion of

nadroparin (a low-molecular-weight heparin, 3,800 units) was prescribed right away and thereafter every 12 hours. Unfortunately, dense right hemiplegia recurred during the infusion, making any further considerations on the tPA therapy apparently unfavorable.

On the following day (July 18), the dense hemiplegia again ameliorated to only mild clumsiness on the right side before 9 am. However, he had at least 5 recurrent episodes of right hemiplegia, each lasting for 20~30 minute, after 9 am. He did not have any significant fluctuation of blood pressure during each episode. At that time his fasting glucose was 107 mg/dl, total cholesterol

**Table.** The chronological table of hemiplegic attacks and the infusion of urokinase

	Duration of each attack and the timing of urokinase infusion		
	Day 1 (July 18)	Day 2 (July 19)	Day 3 (July 20)
00:00~01:00	1 <sup>st</sup> recurrence of hemiplegia		
01:00~02:00			Urokinase 60,000 Unit
02:00~03:00	(Sleep from 01:00~05:00)		■(distal M.P. preserved)
03:00~04:00			■(distal M.P. preserved)
04:00~05:00		(Sleep from 00:00~08:00)	
05:00~06:00			
06:00~07:00			
07:00~08:00	(Returned to mild hemi-		
08:00~09:00	paresis (4/5) before 09:00)		
09:00~10:00			Urokinase 60,000 Unit
10:00~11:00		■(EEG recording)	■(The last attack)
11:00~12:00		■	
12:00~13:00			
13:00~14:00	Totally 5 attacks, each	Urokinase 60,000 Unit	
14:00~15:00	around 20~30 minutes,	■	
15:00~16:00	from 09:00 to 24:00		
16:00~17:00	(on the patient's account,		
17:00~18:00	not recorded in chart)		
18:00~19:00		Urokinase 60,000 Unit	
19:00~20:00		■	
20:00~21:00			
21:00~22:00		■(distal M.P. preserved)	
22:00~23:00		■(distal M.P. preserved)	
23:00~24:00			

Each ■: duration of 5 minutes.

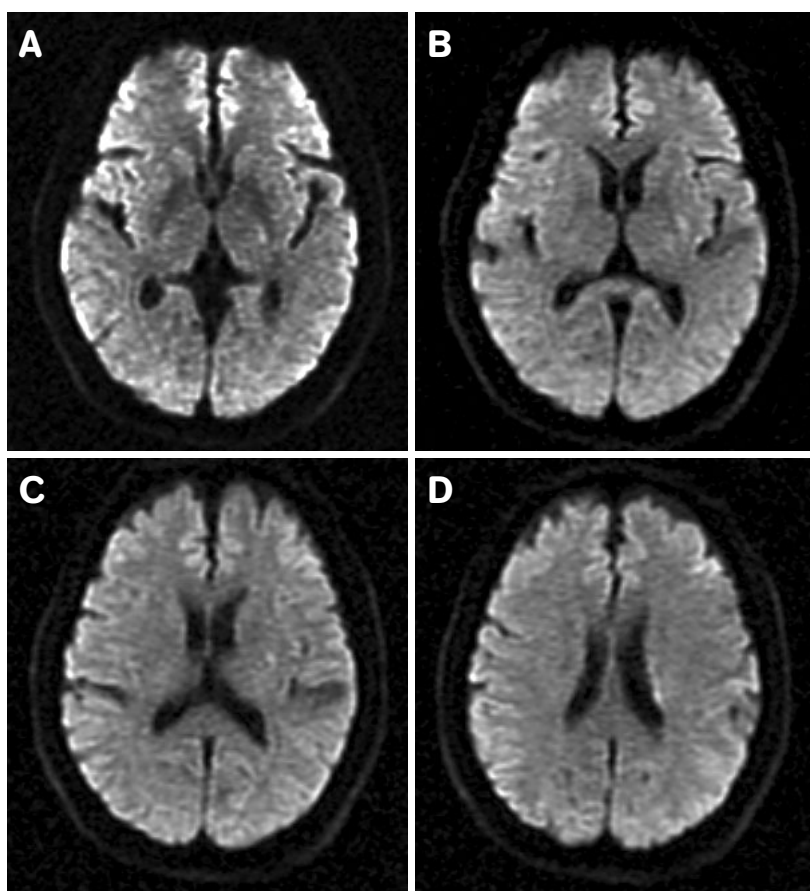
Except for the last attack, the duration and severity of each attack seemed to be diminished after the use of urokinase.

M.P.: muscle power.

231 mg/dl, LDL 180 mg/dl, and HbA1C 4.8%. The prothrombin time, activated partial thromboplastin time, hematocrit, platelet count, white blood cell count, and biochemistry data were all within normal limits. The finding of the brain magnetic resonance image done at 10 am. showed a hyperintensity lesion at the lateral aspect of left thalamus, posterior part of the left globus pallidus and corona radiata on the diffusion-weighted image (DWI) (Fig. 1). The rate of normal saline infusion was therefore adjusted from 40 ml/hr to 80 ml/hr. He also received simvastatin (20 mg daily).

On the third day (July 19), the stereotypical attacks still recurred (Table). There was a 20-minute episode at around 10 am when the patient was under electroencephalographic (EEG) monitoring, which did not show any epileptiform discharge. The patient had another episode of right central facial palsy, hemiplegia,

extensor-type plantar response, increased tendon reflex, and more slurred speech at 11 am right in front of the physicians. However, there was no eyeball deviation, visual field defect, sensory impairment, dysphasia, or hemineglect. Also, no jerky movement, marching of the weakness, headache, or Hoover's sign was noted. We suggested that the patient should take a head-down position right away but the maneuver failed to result in any clinical improvement. Most of these attacks occurred at rest and were preceded by an aura composed of dizziness, nausea, yawning, and a sensation of "it's coming". With the informed consent from the patient and his family, we decided to give intravenous infusion of urokinase 60,000 IU (drip for 30 minutes) every 8 hours in addition to the anticoagulant since 6 pm on July 19 because of the intractably recurring attacks of hemiplegia. After receiving the first dose of urokinase, the patient had another



**Figure 1.** A high intensity signal on the DWI in left lateral thalamus (A to B), posterior globus pallidus (B to C), and posterior corona radiata (D). Note that in figure (B), the image of the spared internal capsule between the two infarction areas looks like a Greek alphabet "Φ".

attack within one hour but retained volitional control of the distal limbs. We continued the intermittent infusion of urokinase, and the patient had four more 10-minute attacks from 9:00 pm July 19 to 4 am July 20. These latter attacks were shorter than before, and characteristically left the volitional control of the distal limbs unaffected.

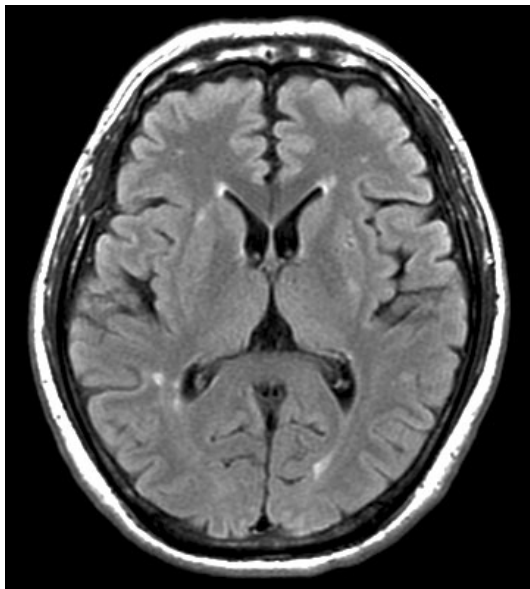
The last attack happened at 10:30 am on July 20 2007 and lasted for 14 minutes. The infusion of urokinase was gradually tapered (every 8 hours for 3 days, then twice daily for 2 days, then once daily for 2 days) and then was discontinued. This patient received aspirin 100 mg and warfarin 1.25 mg daily with the international normalized ratio (INR) kept around 1.21 after one week. CT angiography showed stenoses, all below 60%, in multiple pre-cerebral arteries, and fenestration of the basilar artery. The anterior choroidal and lenticulo-striatal arteries were difficult to be visualized. Extracranial color-coded duplex sonography (ECCD) showed atherosclerotic carotid vessels without significant stenosis or hemodynamic changes. Single photon emission computed tomography (SPECT) of cerebral perfusion showed

mildly decreased perfusion in bilateral basal ganglia and pons. None of the foregoing findings were exactly compatible with the clinical manifestations. The patient was discharged without residual neurological deficits. Thereafter he still had intermittent dizziness for several weeks but had no more hemiplegic attack. Four months later, the T2-weighted image of brain MRI showed a hyperintensity lesion only at the left posterior globus pallidus (Fig. 2).

## DISCUSSION

The case history presented here is compatible with the "CWS" which was first described by Donnan et al. in 1993<sup>(1)</sup>. The syndrome which is characterized by recurrent and stereotypical episodes of motor and/or sensory dysfunction involving face, arm, and leg, is usually associated with a high risk of imminent lacunar infarction with permanent deficits. Our patient and about 70% of the other reported cases have hypertension<sup>(1)</sup>. We observed an aura composed of sensations of "it's coming", "anorexia", or "dizziness" before each attack. Similar symptoms were also reported previously, although some of the patients were initially misdiagnosed as hysterical in nature<sup>(1)</sup>. In a case series of 45 patients, the number of attacks ranged from 13 episodes in 3 days to 7 episodes in 2 hours (mean 4.8 attacks). Our case had totally 15 recurrent attacks within 4 days after an initial cerebral ischemic episode. On the other hand, dural sinus thrombosis has been reported to mimic the CWS clinically<sup>(3)</sup>.

The CWS pathophysiology is complex and unclear. It was reported that small infarcts in the basal ganglia or pons, close to the central motor pathways, appear to be responsible for the primary lesions<sup>(4)</sup>. Hemodynamic changes in the territory of the penetrating arteries, and the other molecular or functional abnormalities such as depolarization affecting adjacent motor pathways, are hypothesized to play a major etiological role<sup>(1)</sup>. High-grade stenoses of penetrating vessels due to different pathologies (such as lipohyalinosis or small atheroma) may ultimately give rise to the hemodynamically critical status. In our patient, we saw an ischemic damage area



**Figure 2.** The follow-up T2-weighted brain MRI four months later. A high intensity signal existed at the posterior part of left lentiform nucleus, near the posterior limb of internal capsule.

with DWI before the recurrence of the following 14 episodes of hemiplegia. The area of ischemia was most likely in the territory of a branch of the left anterior choroidal artery considering the concurrent involvement of the lateral aspect of thalamus, posterior part of the globus pallidus, and posterior corona radiata<sup>(5)</sup>.

Most CWS cases are refractory to conventional therapies including hemodilution, anticoagulant, antiplatelet, or thrombolytic agents, but combinations of high-dose oral clopidogrel and aspirin<sup>(6)</sup> or pharmacological elevation of blood pressure<sup>(7)</sup> have been reported as beneficial in several cases. Our patient had intractably recurrent hemiplegia despite treatment with hydration, intravenous low-molecular weight heparin, head-down position, statins, and oxygen supplement. Interestingly, after the institution of intermittent intravenous infusion of low-dose urokinase (60,000 unit, initially every 8 hours, tapered gradually within 7 days) and concurrent use of anticoagulant and hydration, the duration of attacks shortened, and the severity of attacks attenuated. It seems likely that anticoagulants stabilized the microthrombus whereas urokinase gradually reduced the size of the microthrombus to improve the flow volume in a diseased, stenotic (probably with micro-atheroma) penetrating artery. Our observation also suggests a hemodynamic nature underlying the pathogenesis of CWS. In our patient, the symptoms and signs were probably related to the functional impairment of the internal capsule secondary to the jeopardized blood flow. Since the myelinated and densely packed fiber tracts in the internal capsule are relatively resistant to ischemia, we could only observe significant ischemic injuries in the adjacent structures on DWI. The image of the spared internal capsule between two hyperintensity lesions on the DWI looks like a Greek alphabet “Φ”. Similar observations

had been reported in the literature<sup>(2)</sup>.

In conclusion, we have reported a case of CWS having more recurrent hemiplegic attacks than those ever reported previously. Our case is also highlighted with the observation that urokinase, combined with anticoagulant and hydration, may change the pattern of attacks and may result in a favorable outcome. In view of this single case report, we would suggest further randomized control study to elucidate the therapeutic role of urokinase and heparin in CWS.

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