Capsular Warning Syndrome: Clinical Analysis and Treatment

Ianying he

Second people's Hospital of Chengdu <https://orcid.org/0000-0002-7127-6333>

Ronghua Xu (✉ 2234117052@qq.com)

Jian Wang

The Second People's Hospital of Chengdu

Lili Zhang

Guizhou 2nd Provincial Peoples Hospital

Lijuan Zhang

Nuclear Industry 416 Hospital of Chengdu

Fangfang Zhou

The Second People's Hospital of Chengdu

Weiwei Dong

Chongqing Medical University

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Abstract

Background: Capsular warning syndrome (CWS) was a rare clinical syndrome, which was defined as recurrent transient lacunar syndromes. The mechanism and clinical management of CWS were not clear. The purpose of this study was to discuss the clinical characteristics, treatment and prognosis of the CWS. **Methods:** This was a multicenter retrospective study that involved three medical centers, we collected clinical data from patients with CWS between January 2013 and December 2018. We analyzed the clinical characteristics of the CWS. Patients with CWS were divided into two groups: rt-PA and no rt-PA groups. We analyzed the therapeutic effects and prognosis between different groups. **Results:** This study included 72 patients, 27 in rt-PA group, 45 in no rt-PA group, hypertension and dyslipidemia were the most common risk factors. The mean number of episodes before an irreversible neurological impairment or the symptoms completely disappeared was 5 times(3-11). 59 (81.94%) patients had acute infarction lesions on the diffusion weighted imaging (DWI). The most common infarct location was the internal capsule (76.38%,55), followed by the thalamus and pons. The difference in therapeutic effects between rt-PA, single and double antiplatelet groups was not significant($P>0.05$). A good prognosis was observed in 61 (84.72%) patients at 3-month, 23 (23/27, 85.19%) patients in rt-PA group and 38 (38/45,84.44%) patients in no rt-PA group($P>0.05$). After 3 months of follow-up, 2 patients had recurrent ischemic stroke. **Conclusions:** The most effective treatment of CWS remains unclear. Despite the high incidence of infarction in CWS patients, more than 80% patients had favorable functional prognosis

Background

The term ‘Capsular Warning Syndrome’ (CWS) was first proposed in 1993 by Donnan et al, which was defined as having at least three stereotyped episodes of motor lacunar syndrome (MLS) or sensorimotor lacunar syndrome (SMLS) within 24 h, that involved 2 of 3 body parts (face, arm, or leg) or more without cortical symptoms [1]. Latter studies used a broader 72h time range to define CWS. Other time intervals included 48 h or even seven-days [2,3].

CWS was a rare clinical syndrome, which presented repeated stereotyped episodes of transient ischemic attacks (TIA), and increased the risk of permanent infarction, there had not been many large studies. Previous study showed that the incidence was about 1.5% among patients with TIAs [2]. Therefore, the exact pathophysiological mechanism of CWS was not clear, and different treatments had been suggested, such as blood pressure control [4,5], anticoagulation [6], double antiplatelet therapy [7,8], single antiplatelet, and thrombolytic agent [8-14], but the best clinical management of these patients remain controversial.

In this study, we therefore collected patients with CWS from three medical centers to discuss the clinical characteristics, treatment, and prognosis of the CWS.

Methods

Patients and clinical data

Three authors (LY H, FF Z, LJ Z) reviewed the medical records of all the acute ischemic stroke (AIS) and TIA patients by searching the Electronic Medical Record (EMR) system from three hospitals between *January* 2013 and December 2018. The clinical characteristics of CWS were reviewed by medical records and discharge obtained from primary physicians. When they did not contain adequate information, questionnaires were sent to the physicians by fax.

We defined CWS as the succession of at least three episodes of stereotyped pure motor hemiparesis, pure sensory hemiparesis, sensory motor hemiparesis, or ataxic hemiparesis, with or without dysarthria, which occurs repeatedly within 48h, with complete resolution of symptoms between episodes.

National Institutes of Health Stroke Scale (NIHSS) score was used to assess the severity of stroke at onset. ABCD2 score was used as the index of TIA recurrence, which was calculated at admission.

3-month modified Rankin Scale (mRS) and NIHSS score were obtained from medical records, each primary physician, or face-to-face interview. Good prognosis was defined as $mRS \leq 2$.

Statistical Analysis

Firstly, we summarized the clinical characteristics of all CWS patients. Continuous variables were expressed as mean $\pm$ standard deviation (SD). Categorical variables were expressed as percentile values. Secondly, patients were classified into no rt-PA group and rt-PA group, demographic characteristics and prognosis were compared between the 2 groups in univariate analysis. Continuous variables were compared with Student t test. Categorical variables were compared with chi-square test or Fisher's exact test, distributions of continuous variables were determined by the Kolmogorov–Smirnov test, while Mann–Whitney two sample test was applied in case of non-normal distributions. The data was analyzed using SPSS 22.0 software. P values < 0.05 was considered as statistically significant.

Results

Demographics characteristics of the study subjects

We retrospectively reviewed 4213 patients, among them, 3370 had acute ischemic stroke and, 843 subjects with TIA, which were manually reviewed to identify patients affected by CWS. After reviewing the patient's history, clinical characteristics, risk factors, neuroimaging, 417 AIS patients had stuttering presentations, 171 TIA had stuttering presentations (Figure 1). After manual reviewing, 72 patients were identified (72/4213, 1.71%), comprised 42(58.30%) men and 30 (42.70%) women. The mean age was 66.28 ± 7.90 years (38-96 years).

In the study population, the most common risk factors were hypertension and dyslipidemia, 52 patients had a history of hypertension, 47 had a history of hyperlipidemia, 27 had a history of diabetes, 26 patients smoke,24 current alcohol drinking. 27 patients were treated with rt-PA (rt-PA group), 45 patients (no rt-PA group) were treated with other medical treatment, among them, 30 patients were treated with 300 mg of clopidogrel followed by 75 mg/day and aspirin (100 mg/day) and high-dose atorvastatin (40 mg/day), 15 patients were treated with aspirin (200mg/day) and atorvastatin (40 mg/day).Clinical characteristics of CWS patients were showed in table 1.

Table 1. Clinical characteristics of patients with CWS

	N=72
Age, y(Mean $\pm$ SD)	66.28 $\pm$ 7.90
NIHSS score(Mean $\pm$ SD)	7.90 $\pm$ 2.35
The mean number of episodes(Mean $\pm$ SD)	5.31 $\pm$ 2.22
Mean Duration(Mean $\pm$ SD)	24.11 $\pm$ 11.21
ABCD2 score(Mean $\pm$ SD)	4.57 $\pm$ 1.28
Females,n(%)	30(41.67)
Men,n(%)	42(58.33)
BMI $\geq$ 24 kg/m, n(%)	16(22.22)
Hypertension,n(%)	52(72.22)
Current Smoking,n(%)	26(36.11)
Current alcohol drinking,n(%)	24(33.33)
Diabetes, n(%)	27(37.50)
Hyperlipidemia,n(%)	47(65.28)
Family history of stroke,n(%)	16(22.22)
Medications use	
Antiplatelet, n(%)	22(30.56)
Antihypertensive, n(%)	31(43.06)
Lipid-lowering medications, n(%)	36(50.00)
Lacunar syndrome	
Pure motor hemiparesis, n(%)	32(44.44)
Pure sensory hemiparesis, n(%)	12(16.67)
Sensory motor hemiparesis, n(%)	24(33.33)
Ataxic hemiparesis, n(%)	4(5.56)
Infarct location	
Internal capsule,n(%)	41(70.69)
Pons,n(%)	5(8.62)
Striatum,n(%)	2(3.44)
Thalamus,n(%)	7(12.07)
Midbrain,n(%)	3(5.17)
Treatment	
Rt-PA,n(%)	27(37.50)
Double Antiplatelet,n(%)	30(41.67)
Single Antiplatelet,n(%)	15(20.83)

Clinical characteristics

The mean NIHSS score was 7 (range2-12) at onset. 59 patients (81.94%) had elevated blood pressure when admitted to stroke ward. The mean systolic pressure was 169.30mmHg. 32(44.44%) patients were pure motor hemiparesis,24(33.33%) patients were sensory motor hemiparesis. The mean number of episodes before an irreversible neurological impairment or the symptoms completely disappeared was 5 times (3-11). The duration of these episodes was different, an average of 24 minutes (range2-50). After

CWS, permanent neurological impairment occurred in 52 (72.22%) patients, and symptoms completely disappeared in 20 patients (27.78%).

Laboratory and Neuroimaging examinations

28 patients had hyperlipidemia at admission. Carotid artery ultrasonography showed that 41(56.94%) patients had mild carotid artery plaque. No arrhythmia was found during ECG monitoring, and echocardiography did not show any cardiac embolic sources in the patients. All patients were subjected to brain CT at admission. Cranial CT showed no acute cerebral infarctions at admission. Intracranial and extracranial vascular were evaluated through computed tomography angiography (CTA) in all patients, which performed within 5 days at admission. Cranial CTA showed no severe stenosis or dissection in all patients, echocardiography did not show any cardiac sources, therefore, we speculated that the pathogenesis of CWS was related to arteriosclerosis of small-penetrating vessel. All patients measured blood pressure every 20 minutes, 59 (81·94%) patients exhibited hypertension when admitted to the stroke ward.

Brain MRI performed 12-48 h after admission in all patients, 58 patients had an acute infarction on DWI, the most frequent infarct area was internal capsule (41, 70.69%). Other locations were in the thalamus (7, 12.07%), pons (5, 8.62%), the midbrain (3, 5.17%), the striatum (2, 3.44%).

Treatment

27 (37.50%) patients were treated with rt-PA in the acute phase of CWS, who were treated with antiplatelet therapy (aspirin or clopidogrel) after 24h when hemorrhage was excluded by CT examination. 45 patients were treated with other medical treatment, including antiplatelet (30 double antiplatelet,15 single antiplatelet), lipid-lowering medications and blood pressure control. Baseline characteristics of patients in the no rt-PA group and rt-PA group were compared (Table 2). Age, NIHSS and mean number of episodes were higher in no rt-PA group than rt-PA group, but there was no statistical difference($P>0.05$). There were no significant group differences in the percentage of hypertension, diabetes and hyperlipidemia ($P>0.05$).

Table 2. Comparison of baseline characteristics between patients with no rt-PA and rt-PA groups.

	no rt-PA group (45)	rt-PA group (27)	P*
Age, y(Mean SD)	67.24±8.27	64.69±7.11	0.179
NIHSS score at onset(Mean SD)	7.47±2.24	6.48±2.44	0.088
The mean number of episodes	5.76±2.44	4.74±2.31	0.142
Mean Duration	23.91±11.08	24.4±11.64	0.926
ABCD2	4.58±1.34	4.56±1.19	0.967
Females, n (%)	19(42.22)	11(40.74)	0.902
Men, n (%)	26(57.78)	18(66.67)	0.789
BMI≥24 kg/m, n (%)	9(20.00)	7(25.93)	0.558
Hypertension, n (%)	32 (71.11)	20(74.07)	0.786
Current smoking, n (%)	18(40.00)	8(29.63)	0.375
Diabetes, n (%)	16(35.57)	11(40.74)	0.660
Hyperlipidemia, n (%)	30(66.67)	17(62.96)	0.749
Current alcohol drinking, n (%)	15(33.33)	9(33.33)	1.00
Family history of stroke, n (%)	9(20.00)	7(25.93)	0.558
Medications use			
Antiplatelet, n (%)	14(31.11)	8(29.63)	0.895
Antihypertensive, n (%)	19(42.22)	12(44.44)	0.854
Lipid-lowering medications, n (%)	25(55.56)	11(40.74)	0.224

*Comparison between no rt-PA and rt-PA groups. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as percentile values. Continuous variables were compared with Student t test. Categorical variables were compared with chi-square test or Fisher's exact test, distributions of continuous variables were determined by the Kolmogorov-Smirnov test, while Mann-Whitney two sample test was applied in case of non-normal distributions.

No bleeding complications occurred in the rt-PA group. 17 patients presented new episodes after rt-PA treatment. 22 patients had ischemic infarction. 10 patients showed a complete recovery. No rt-PA group received antiplatelet treatment (aspirin or clopidogrel or aspirin+clopidogrel), 30 patients were treated with a loading dose of 300 mg of clopidogrel followed by clopidogrel 75 mg and aspirin 100mg every day and daily high-dose atorvastatin, 15 patients were treated with single antiplatelet treatment (75 mg clopidogrel or 200mg aspirin) and high-dose atorvastatin every day. 35 patients presented new episodes in no rt-PA group; 10 patients showed a complete recovery. 36 patients had an acute infarction in DWI in no rt-PA group, 24 patients in double antiplatelet group, 12 patients in single antiplatelet. The difference in therapeutic effects between rt-PA, single and double antiplatelet groups was not significant ($P>0.05$) (Table 3).

Table 3. Comparison of therapeutic effects between rt-PA, single and double antiplatelet

	single antiplatelet group (15)	double antiplatelet group(30)	rt-PA group (27)	P*
New episodes after treatment, n (%)	11(73.33)	24(80.00)	17(62.96)	0.356
Complete recovery, n(%)	4(26.67)	6(20.00)	10(37.04)	0.356
Acute infarction, n (%)	12(80.00)	24(80.00)	22(81.48)	0.998

*Comparison between rt-PA, single and double antiplatelet. Categorical variables were expressed as percentile values. Categorical variables were compared with chi-square test or Fisher's exact test.

61 patients (84.72%) had a good outcome at 3-month, 23 patients in rt-PA group, 38 patients in no rt-PA group (22 in double antiplatelet, 13 in single antiplatelet). Compared with the baseline, NIHSS score of the 3-month decreased both in two groups. There was no significant difference in 3-month prognosis between the two groups ($P>0.05$)(Table 4).

Table 4 Prognosis of CWS patients in no rt-PA and rt-PA groups at 3-month

	no rt-PA group(45)	rt-PA group (27)	P*
mRS $\leq$ 2	38(84.44)	23(85.19)	0.933
NIHSS score	3.49 $\pm$ 1.84	3.26 $\pm$ 2.05	0.682

* Comparison between no rt-PA and rt-PA groups. Continuous variables were compared with Student t test. Categorical variables were compared with chi-square test.

Discussion

CWS was a rare clinical syndrome, which had not been extensively studied. In previous studies showed that the incidence of CWS in TIAs patients was only 1.5% to 4.5% [1-3]. In different studies, the time lapse used to define what was considered CWS was highly variable. In our study, we included patients with recurrent lacunar syndromes up to 48h from the first episode. The incidence in AIS/TIAs was 1.71%, which appears to be consistent with previous studies.

CWS was characterized by an abrupt onset of symptoms, the duration of each episodes was variable, one study showed that the mean duration of each episode was 6.1 minutes [1]. In this study, patients with recurrent TIA presentations within several hours from the first episode, symptoms completely improved within 2-50 minutes, the mean duration of CWS was 24 minutes. CWS was generally manifested as repetitive lacunar syndrome, although some authors had reported that CWS might be associated with other symptoms, such as sensory dullness and ophthalmoplegia [15]. The most frequent symptom was MLS. In the past study, Donnan et al. recruited 50 patients with CWS, the percentage of MLS was 50% [1], and Camps-Renom et al. reported that MLS accounted for 61.9% of 42 CWS [16]. In our study, 32 patients

were mainly manifested as pure motor hemiparesis, and 24 patients were manifested as sensory motor hemiparesis, the incidence of pure motor hemiparesis/sensory motor hemiparesis was 77.78%, our finding was consistent with a recent study [17].

CWS had a high risk of developing ischemic stroke with a permanent deficit, 7-day stroke risk following CWS was as high as 60%, this rate rises to 71.2% with routine use of MRI [2]. In our study, 58(80.56%) patients had an acute infarction on DWI, the result was consistent with previous studies. The most frequent location was internal capsule (50%) [16,18]. With the wide use of MRI, some studies showed that ischemic lesion could occur at other location. In our study, that area of 41(70.69%) patients's infarction was the internal capsule, other area of infarction was in the thalamus, midbrain, pons, striatum. Therefore, the applicability of the term "Capsular warning syndrome " was inadequate, "Vascular warning syndrome" or "Stroke warning syndrome" might be more appropriate

Studies had confirmed that hypertension, diabetes, dyslipidemia, smoking and other common stroke risk factors were related to CWS, which might suggest that atherosclerosis was involved in the pathogenesis of CWS. However, the exact pathophysiological mechanism of CWS was not clear. Some authors had speculated that CWS was most likely to be ischemia due to in situ small-penetrating vessel disease, and some authors believed that intermittent hemodynamic changes secondary to structural arterial changes or hypertension might be the most likely mechanism of CWS[1,19]. In our study, cranial CTA showed that vascular stenosis or dissection was not found in patients, echocardiography did not showed any cardiac sources, therefore, we further confirmed that the pathogenesis of CWS was related to arteriosclerosis of small-penetrating vessel, but the mechanism of symptoms fluctuate remains unclear.

There was some debate about the most effective treatment in the acute phase of CWS. Despite various treatments being available and used, it was unclear whether these treatments alter the natural course of the syndrome. Intravenous thrombolysis, double antiplatelet therapy, single antiplatelet therapy, anticoagulants, vasopressors had been used to treat patients with CWS[1,4,5,7,9-13,20-28], it remains uncertain whether any of these therapies were able to change the progression of the syndrome. There was no strong evidence for the efficacy of anticoagulant therapy in the acute phase of CWS. There had been case series suggesting that double antiplatelets (aspirin add clopidogrel) might be beneficial, similar to the effect seen in acute coronary syndromes [7,27,28]. In a case series including two patients with CWS, it was reported that following the start of double antiplatelets, there was no progression of symptoms. However, there were also reports that double antiplatelets could not prevent infarction. In a recent study, 17 patients with stuttering lacunar syndrome(SLS) were treated with double antiplatelets, a loading dose of 300mg of clopidogrel was administered along with aspirin in all cases, symptoms improved in 11 patients, so the authors suggested that double antiplatelets appeared effective for the acute treatment of SLS[17]. In our study, 25 patients suffered from infarction despite receiving double antiplatelets therapy. Therefore, the effectiveness of double antiplatelet therapy on CWS needs to be confirmed by randomized controlled trials.

There was little evidence about whether thrombolysis was beneficial in CWS. In some studies showed that CWS patients were treated with thrombolysis, the symptoms completely disappeared, so some scholars considered that rt-PA could be effective[29,30]. However, a recent study showed no significant benefit in functional outcomes in 9 patients receiving intravenous thrombolysis compared with 9 patients not receiving thrombolysis [3]. In our study, 27 patients were treated with intravenous rt-PA. 45 patients were treated with no rt-PA. Age, NIHSS and mean number of episodes were lower in r-tPA group than no r-tPA group, the difference might be related to our sample size, the number of patients in the r-tPA group was small, the patients who received r-PA were younger, and had mild symptoms, but there were no statistical difference in two groups ($P>0.05$) Although the difference in therapeutic effects between rt-PA, single and double antiplatelet groups was not significant, patients who receive rt-PA seemed to have more frequent complete recovery and fewer new episodes after treatment(Table 3). In this setting, rt-PA should be the therapeutic choice when patients with CWS present within the therapeutic time window with disabling symptoms.

Finally, one of the aims of our study was to analyze the prognosis of patients with CWS. In our study, a favorable outcome was observed in 61 (84.72%) patients at 3-month, 23 patients (23/27,85.19%) in rt-PA group and in 38 (38/45,84.44%) patients in no rt-PA group. There was no difference in functional outcome at 3 months between the two groups. In general, intravenous thrombolysis was safe for CWS patients, and no bleeding complications had been reported. Due to the small number of patients, the effect of rt-PA in CWS must be further confirmed in clinical studies.

Some limitations of this study merit consideration. This study updated and added some new information about CWS, although our study was a multicenter retrospective study, as CWS was a rare clinical disease and the number of patients included was small, which may affect the results of the study. We may need to further expand the number of patients and further explore the relationship between CWS and hemodynamic changes to find the best treatment for CWS.

Conclusions

In conclusion, CWS was a rare clinical syndrome, which describes recurrent stereotyped lacunar transient ischemic attacks clustered within a short period of time and was associated with a high risk of developing a completed stroke. The mechanism of CWS had not been fully elucidated. Various treatments being available and used to CWS, the optimal treatment was not clear, despite the high incidence of infarction in CWS patients, most patients had a good prognosis at 3 months.

Abbreviations

CWS: Capsular warning syndrome; SLS:Stuttering lacunar syndrome; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; CTA: computed tomography angiography; SD: Standard Deviation

Declarations

Ethics approval and consent to participate

We obtained ethical approval for this study from the Medical and Health Research Ethics Committee in Second people's Hospital of Chengdu, the Second Affiliated Hospital of Chengdu College, Nuclear Industry 416 Hospital of Chengdu, and Chongqing Medical University. All patients gave an informed consent to study participation. All the pertinent guidelines required by our institution for the preparation of retrospective studies have been followed.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LYH, FFZ, LJZ were responsible for data collection and the first draft of the paper and further manuscript. RHX and JW was responsible for design of the study. WWD was responsible for overseeing the concept and design of the study, the data analysis and interpretation, and writing the paper. LLZ was responsible for data collection. All authors read and approved the final manuscript for publication.

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Figures

Figure 1

Figure 1. Patients' flowchart