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Thrombolysis in Capsular Warning Syndrome

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Introduction

Capsular warning syndrome (CWS) was first described in 1993 in patients who presented repeated episodes of subcortical transient ischemic attacks [1]. In 42% of the patients this led to infarct. CWS has been related to small penetrating vessel alteration, but its real pathophysiology is as yet unknown. Many different theories have been suggested, including hemodynamic alteration due to lipohyalinosis, microatheromatosis, vasospasm or embolism from the heart or artery to artery [2].

Different treatment modalities have been proposed, induced hypertension being the most widely used and the best described. Intravenous heparin and antiplatelet treatments have also been applied, without any conclusive results. The efficacy of intravenous thrombolysis has not been previously reported.

Materials and Methods

From February 2005 to December 2006 we prospectively registered the clinical and demographic data of 4 patients with a diagnosis of CWS admitted to our department. In this period 863 patients with ischemic stroke were admitted. These 4 patients with CWS represented 0.46% of all.

All 4 patients, before being treated with rt-PA, presented at least 3 stereotyped episodes of pure motor or sensorimotor stroke, involving the face, arm and leg simultaneously, or any 2 of these, without any cortical signs in the past 24 h. The following data were compiled: age, race, sex, vascular risk factors (hypertension, ischemic heart disease, diabetes mellitus, hypercholesterolemia, atrial fibrillation and smoking).

All patients were asymptomatic at admission. They stayed at the stroke unit to monitor blood pressure and neurological status. A CT scan and an ultrasound examination of the brain-supplying arteries were performed prior to rt-PA administration, as well as blood tests and 12-lead ECG. rt-PA was administered during the last new episode of neurological deficit, with a score of >7 on the National Institute of Health Stroke Scale (NIHSS) in all cases, assuming ischemic etiology. Eligibility was restricted according to Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) [3] criteria, in patients admitted within 3 h of stroke onset and between 18 and 80 years of age. The patients received treatment with intravenous alteplase (rt-PA) at a dose of 0.9 mg/kg. CT scan was repeated 24 h after thrombolytic treatment. Conventional magnetic resonance imaging (MRI) and diffusion-weighted MRI (DWI) were performed between 2 and 6 days after rt-PA treatment. Stroke etiology was defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [4].

Results

The mean age was 67.5 years, with standard deviation (SD) = 10.7 and range = 57–81. Three patients were men. All were Caucasian. The patients' clinical and outcome data are summarized in table 1. The mean duration of neurological episodes was 19.8 min (SD = 6.7). The mean number of episodes was 4 (SD = 1.4). The median initial NIHSS score was 10 (q1–q3: 7.5–13). During monitoring in the stroke unit all patients had repeated clinical attacks (from 1 to 2). No episode was related to blood pressure alterations. rt-PA was started assuming that the new neurological deficits were associated with a new subcortical transient ischemic attack in the CWS context and also assuming that the possibility of an intracerebral hemorrhage is very low in patients with a normal CT scan who fulfilled the CWS criteria. Transcranial Doppler was performed and no arterial occlusion was present. A CT scan performed after 24 h showed no hemorrhagic signs in any of them.

After thrombolytic treatment, 3 patients had a complete recovery without new episodes during follow-up (NIHSS score = 0 at discharge) and a normal MRI without DWI lesions. One patient experienced a new episode (after remaining asymptomatic for 10 h since thrombolysis had been administered) with severe motor weakness (NIHSS score = 12), without complete posterior recovery, showing an acute lesion at DWI. The mean time of discharge was 6 days (SD = 3.8), range = 3–11, 4.33 (SD = 2.3) in asymptomatic patients and 11 in patients with residual deficit.

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Table 1. Clinical and demographic data

	Case 1	Case 2	Case 3	Case 4
Age, years	81	57	57	75
Sex	male	male	male	female
Vascular risk factors	HLP, DM, IHD, AF	SMK, HT, HLP	HT, HLP	HT
Previous episodes	3	6	3	3
Symptoms	motor	motor	sensitive motor	sensitive motor
Initial BP, mm Hg	147/87	170/100	181/102	144/75
NIHSS in last episode	12	9	11	9
NIHSS at discharge	0	0	0	12
mRS at admission	0	0	0	0
mRS at discharge	0	0	0	4
MRI-DWI	on day 6: no lesions on DWI	on day 3: no lesions on DWI	on day 2: no lesions on DWI	on day 5: right capsular retrolenticular lesion (23 × 13 × 28 mm)
Onset of first episode, hours before coming to the hospital	5	6	6	10
Last episode, minutes before rt-PA administration	45	30	40	45

HLP = Hyperlipidemia; DM = diabetes mellitus; IHD = ischemic heart disease; AF = atrial fibrillation; SMK = smoke; HT = hypertension; mRS = Modified Rankin Scale; DWI = diffusion-weighted imaging.

Discussion

To our knowledge, there have been no previous reports concerning intravenous thrombolytic treatment in CWS. Pressure therapy (mainly phenylephrine) has been suggested as the treatment of choice [5]. The assumption of its benefit is based on the distal hypoperfusion hypothesis of the penetrating vessel, related to blood pressure fluctuations. In our study, none of the patients presented blood pressure decrease during episodes. Another theory suggests the role of an intermittent peri-infarct depolarization, which affects motor pathways adjacent to the infarct due to metabolic alterations. This has been demonstrated in animals but not in humans [6]. Anticoagulant treatment with heparin has also been used [1, 6]. One article reported the effect of a loading dose of clopidogrel plus acetylsalicylic acid in 2 patients with aspirin-resistant CWS [7]. In summary, no conclusive data could be obtained from these reports.

At the present time, intravenous thrombolysis with rt-PA still is the only approved therapy for acute ischemic stroke. The use of rt-PA in patients with rapid neurological improvement remains controversial. However, it is known that one third of these nontreated patients presented an early neurological worsening after initial improvement. On the other hand, rt-PA administration in patients with rapid neurological improvement has been demonstrated to be safe and useful [8]. Thrombolysis in lacunar infarcts is also controversial; it is said that because of the underlying pathogenesis mechanisms, they are not susceptible to pharmacologic reperfusion [9]. Also, some authors have questioned the efficacy of thrombolysis in stroke patients without acute artery occlusion determined in ultrasonographic study. The European Cooperative Acute Stroke Study (ECASS) substudies have, however, demonstrated that those patients also benefit from rt-PA treatment [10]. In our cases we thought that the potential hemorrhagic risk of rt-PA treatment would be well assumed by its potential benefit, especially in view of the high rate of stroke development. CWS mechanism could be related to an intermit-

tent hypoperfusion in penetrating vessel distal territory probably due to a thrombus progression, without any blood pressure changes as in this study. In this situation, rt-PA action could prevent the final established stroke. This possibility may be supported by the fact that thrombolysis-treated patients which remained asymptomatic did not show any acute lesion in MRI-DWI after treatment [6].

Although there is a clear relationship between the use of rt-PA and clinical improvement, we cannot definitely exclude spontaneous recanalization in these cases.

Conclusion

CWS remains an unresolved neurological situation in which rt-PA treatment might play a useful and safe role. Therefore, more studies are necessary to clarify the physiopathology of CWS in order to use the most accurate treatment, taking into account the high rate of patients that finally develop a subcortical infarct.

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