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BRIEF COMMUNICATION **KISA RAPOR**

CAPSULAR WARNING SYNDROME: CASE REPORT

Özge TÜRK, Vedat Ali YÜREKLİ, Nihat ŞENGEZE

Süleyman Demirel University Faculty of Medicine, Department of Neurology, Isparta, TURKEY

ABSTRACT

Capsular warning syndrome (CWS) is a rare clinical syndrome, which is defined as a recurrent transient lacunar syndrome. Because of its pathophysiology remains unclear, most effective treatment still cannot be defined. Here, we purposed to discuss three patients who presented with CWS followed with different treatment protocols
Keywords: Capsular warning syndrome, transient ischemic attack, stroke.

KAPSÜLER UYARI SENDROMU: VAKA RAPORU

ÖZ

Kapsüler uyarı sendromu (KUS), tekrarlayan geçici bir laküner sendrom olarak tanımlanan, nadir görülen bir klinik sendromdur. Patofizyolojisi hala yeterince anlaşılamayan bu sendromun en etkili tedavi konusu da belirsizliğini korumaktadır. Kliniğimizde takip edilen üç olgumuzda farklı tedavi protokolleri ile izlenmiş olup nadir görülmesi ve yönetimin zor olması nedeniyle sunmayı amaçladık.
Anahtar Sözcükler: Kapsüler uyarı sendromu, geçici iskemik atak, inme.

Address for Correspondence: Özge Türk, MD. Süleyman Demirel University Faculty of Medicine Department of Neurology, 32260 Isparta - Türkiye.
Phone: +90246 211 20 700 **E-mail:** trkozge1@gmail.com
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ORCID IDs: Özge Türk 0000-0002-8115-6394, Vedat Ali Yürekli 0000-0002-2042-4463, Nihat Şengeze 0000-0002-2821-3708.
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INTRODUCTION

The concept "capsular warning syndrome (CWS)" was first defined by Donnan et al. in 1993. It defines a recurring transient ischemic attack (TIA) with a high risk of an infarct. It is characterized by the recurring stereotypic sensorimotor symptoms affecting the face, arm, and leg without cortical involvement, which emerge within seven days following TIA. The occurrence of at least three motor or sensorimotor symptom episodes within 4 hours and full recovery of two of the three involved body parts (face, arm, or leg) within these episodes is another descriptive characteristic of this syndrome (1,2). If it involves ischemia of the middle and anterior cerebral arteries, it is called capsular warning syndrome (CWS), and if it affects the posterior circulation, it is called pontine warning syndrome (PWS). Several mechanisms such as small vessel disease, embolism from artery to artery, hemodynamic instability, and peri-infarct depolarization may explain the pathophysiology of this syndrome (2). Although this syndrome is associated with a positive functional outcome, the stereotypic and recurrent stroke attacks may concern both patients and clinicians. In this paper, we presented three cases, that were under follow-up due to CWS. Written consents have been obtained from all patients.

CASE REPORT 1

The 52-year-old male patient has applied with a 2-3-minute lasting speech disorder and paresthesia in the right upper and lower extremities to the hospital. In his medical history, genetic mutations were determined: Prothrombin heterozygosity, MTHFR homozygosity, and FV Leiden heterozygosity. He did not use any medication except warfarin. The patient was examined in the emergency unit and the neurological examination showed that his general condition was good, and he was in full cooperation and orientation. All neurological examination findings were normal except for the central-type facial asymmetry on the right side and mild dysarthria. His NIHSS score was 3 at admission and the diffusion magnetic resonance imagining (MRI) showed a lesion consistent with the acute ischemia in the left caudate nucleus and the anterior of the lentiform nucleus (Figure 1). After the examination, the patient was hospitalized in our clinic for follow-up. It was found out that the patient has applied to the hospital with complaints of speech disorder, and paresthesia in the right upper extremity and was diagnosed with cerebrovascular disease. The etiological investigation of the patient with carotid cerebral tomographic angiography and cardiac functions revealed normal findings. The markers of vasculitis were negative. LDL cholesterol level was 193 mg/dl.

Warfarin sodium treatment was initiated as he had the abovementioned thrombophilia risk factors regarding his genetic profile.

Following the hospitalization in our clinic, the patient had 6 hemiparesis attacks on the right side within the first 72 hours, which lasted approximately 2 minutes each (level 1/5-2/5), and had complaints related to dysarthria. The neurological examination of the patient recovered fully at the end of the 2-3 minutes, and the diffusion MRI examination did not show any increase in the ischemia findings. The simultaneous measurements of arterial pressure were normal.

The NIHSS score was 0 in the follow-up examinations. After the initiation of the treatment with warfarin sodium, 100 mg salicylic acid, and atorvastatin, no similar complaints recurred during the follow-up controls. After three months, the patient is still under follow-up with a modified Ranking Scale (mRS) score of 0.

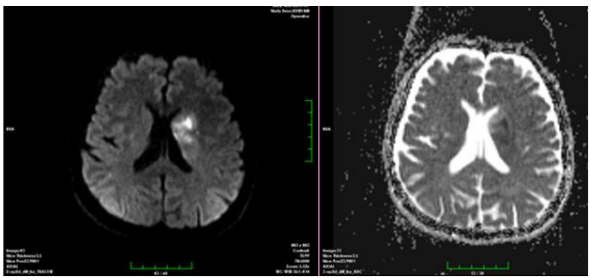

Figure 1. In the diffusion MRI examination, acute diffusion restriction in the left caudate nucleus and the anterior of the lentiform nucleus.

CASE REPORT 2

The 75-year-old male patient had applied to another health center with complaints of weakness and paresthesia in the left arm and leg. As the diffusion MRI examination displayed acute ischemia in the posterior leg of the internal capsule, intravenous tissue plasminogen activator (tPA) treatment was initiated. Since an increase in

muscular weakness was observed during the follow-up, the patient was referred to us for mechanic thrombectomy (Figure 2). Regarding the medical history, the patient had no other pathology except for diabetes mellitus, chronic obstructive lung disease, and hyperlipidemia. During the examination in the emergency unit, the patient had a good general status, was alert, cooperated, and oriented. He had mild dysarthria. The pupillae were normoisocoric and the ocular movements were normal in every direction. A central-type facial asymmetry was observed on the left side. On the left side, muscular strength was at level 4/5, and hemihypoesthesia was observed. The NIHSS score was 4 at admission, and an increase in the muscular weakness in the left upper and lower extremities and dysarthria were observed during follow-up. The patient, whose NIHSS score regressed to 6, was referred to cerebral angiography during his last attack. No major occlusion was observed in the imagining. 8 mg intraarterial tPA was administered. Rapid recovery was observed in the patient's clinical status. During the follow-up, the cranial tomographic examination did not display any hemorrhagic transformation. LDL cholesterol level was 245 mg/dl. Regarding the etiological investigation of cardiac parameters, the ejection fraction was 45% in the echocardiographic examination and the electrocardiography showed normal sinusoidal rhythm. A treatment including acetylsalicylic acid, 75 mg clopidogrel, and atorvastatin was initiated. After three months, the patient is still under follow-up with a Ranking Scale (mRS) score of 0.

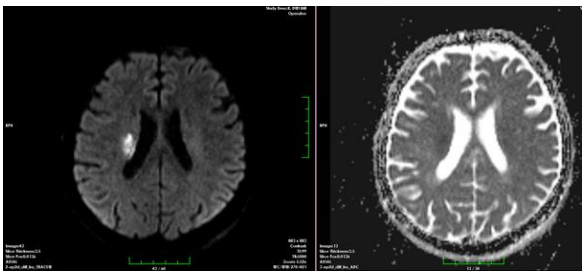

Figure 2. In the diffusion MRI examination, diffusion restriction with acute ischemia in the posterior leg of the right internal capsule.

CASE REPORT 3

It was found out, that the 34-year-old male patient, who had no known comorbidity, had applied to another health center with complaints of speech disorder, paresthesia in the right arm and leg, and weakness. It was also determined that the patient had a complaint of weakness and paresthesia in the right lower and upper extremities 2 hours before these complaints, which lasted 5 minutes. The simultaneous measurement showed a systolic pressure of 160 mmHg. In this health center, the NIHSS score was 4 and the patient was referred to our center for interventional treatment and further investigation following the administration of an intravenous thrombolytic agent (55 mg). At admission to our department, the neurological examination did not reveal any other finding except for promotor drift in the right upper extremity. The diffusion imagining showed diffusion restriction in the posterior leg of the left internal capsule consistent with acute ischemia (Figure 3). No major vascular occlusion was determined in the carotid cerebral computed tomographic angiography. The etiological investigation for cardiac parameters did not show any pathological findings in the electrocardiography, echocardiography, and rhythm Holter monitoring. There were no prominent pathological findings in the genetic and vasculitic examinations. The LDL cholesterol level was 220 mg/dl. The complaints of the patient did not recur during the follow-up in our clinic. Bleeding was observed in the follow-up cranial tomography. A treatment including acetylsalicylic acid, clopidogrel, and atorvastatin was initiated. After three months, the patient is still under follow-up with a Ranking Scale (mRS) score of 0.

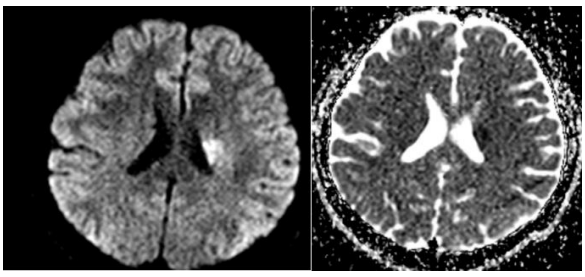

Figure 3. In the diffusion MRI examination, diffusion restriction in the posterior leg of the right internal capsule was consistent with acute ischemia.

DISCUSSION AND CONCLUSION

The clinical characteristics of the capsular warning syndrome are unilateral motor and/or sensorial disorders involving at least two of the

body parts (face, arm, or leg). The most common presentation of the syndrome is isolated motor hemiparesis affecting the face, arm, and leg. There is no evidence related to the cortical findings (3,4). Paul et al. used the capsular warning syndrome (CWS) for the definition of the patients, who had motor lacunar CWS more than one time within seven days after the initial CWS attack, without regarding whether the stroke occurred in the anterior or posterior circulation (5).

In the CWS, the internal capsule in the subcortical region and pyramidal tract at the pons level is affected. While the penetrating vessels of the internal carotid arterial circulation are affected in CWS, the penetrating basilar arteries are affected in PUS.

CSW is 60.9% more common in males compared to females. CWS is more common in individuals in their sixties as risk factors like hypertension, dyslipidemia, smoking, and diabetes are more common at these ages. Stroke and atrial fibrillation are among the less common risk factors associated with CWS. According to the TOAST classification, small vessel disease seems to be the most common etiological factor (3,6). This syndrome is important as there is a high risk of ischemic stroke with a persistent deficit (3,7). In the population studies, it was reported that the risk of stroke was 60% within seven days after CWS (5).

The definitive pathophysiology was not elucidated yet. Some authors suggested that this syndrome was most probably associated with ischemia due to in situ small penetrating vessel disease (3). Renom et al. reported that 73.8% of 42 CWS cases had small vessel disease (6). Regarding different studies, large vessel atherosclerosis was observed in 5%-17% of the cases (5-8). The cardio-embolic mechanisms were determined in at least 4%-12.9% of the cases (5,6). In another theory, it was proposed that this syndrome might depend on the hemodynamic changes within the scope of the penetrating arteries. These hemodynamic changes may become particularly important if there is a structural arterial change within the penetrating vessel like atheroma and/or lipohyalinosis (3). The peri-infarct depolarization is another considered mechanism. The accumulation of the metabolic byproducts of ischemia may trigger temporarily the peri-infarct depolarization and explain the fluctuating structure of CWS. It was demonstrated that the peri-infarct depolarization led to a temporary energy deficit in the ischemic penumbra as a result of the hypoxia and hypotension triggered by the release of the neurotoxic substances from the infarct center (9). It was shown that the biomarkers like adenosine, glucose, glycogen and lactate were correlated with the spontaneously spreading depression in animal models (10,11). However, human studies are still inconclusive. The most effective treatment of this syndrome, whose pathophysiology is still not clarified, is also uncertain. It was reported that intravenous thrombolytic treatment is safe in these patients (12). We also preferred intravenous and intraarterial thrombolytic treatment in our second case. There are also a limited number of studies suggesting that intravenous tirofiban treatment might be also effective.

The recovery of endothelial dysfunction, an increase in the nitric oxide bioavailability, antioxidant properties, inhibition of the inflammatory response, and stabilization of the atherosclerotic plaques are among the pleiotropic effects of statins. The statin treatment decreases the risk of stroke and other cardiovascular events in patients with high cardiovascular risk and atherosclerotic disease. It was observed that the lipid-lowering and pleiotropic properties of atorvastatin contribute to these effects (14-16). In our cases, we preferred atorvastatin treatment as the LDL cholesterol levels were elevated depending on the pleiotropic effects.

More than 80% of CWS patients have a positive functional prognosis independent of the increased infarct incidence (12). We did also not observe any recurrence of ischemic attack during the follow-up after the early period.

In conclusion, as of today, there is no randomized and controlled study focused on CSW patients. Most of the studies are case report series. Therefore, there is no consensus yet on effective treatment. The patients should be carefully followed because of the potential of a completed stroke. Although the risk of a completed stroke is high, most patients have a good prognosis after three months, as in our cases.

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Ethics

Informed Consent: The authors declared that informed consent was signed the patients.

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