Cerebral Infarction in Young Marijuana Smokers – Case Reports

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ABSTRACT

Introduction: Causality of marijuana abuse with development of ischemic stroke has been indicated by numerous case reports and epidemiological studies. As a possible pathophysiological mechanism, the most common consideration is cardiac embolization during paroxysmal atrial fibrillation, systemic hypotension or multifocal intracerebral vasoconstriction. Case reports: We present three case reports of marijuana consumers who were admitted to our comprehensive stroke center due to ischemic stroke within 18-month period of our investigation. In one case, the cause of stroke was not related to the use of marijuana, it was a manifestation of antiphospholipid syndrome. In two cases the association with the abuse of this drug is probable but not certain. In both these cases, an isolated occlusion in vertebrobasilar arterial system was detected, without finding of a cerebral vessels stenosis. Although we did not register the atrial fibrillation, we consider cardiac embolization as probable etiological mechanism of stroke in both cases. In one case, paradoxical embolization due to the persistent foramen ovale represents another potential etiological mechanism. Conclusions: Cannabinoid use may cause ischemic stroke, especially in the younger age category. Therefore, in these patients we recommend focusing on the history of cannabinoid abuse and carry out toxicological urine tests.

KEYWORDS

cannabinoids; ischemic stroke; young stroke; reversible cerebral vasoconstriction syndrome; vasospasms

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INTRODUCTION

The association between marijuana use and the occurrence of ischemic stroke (IS) is widely discussed in the literature. Westover et al. (1) were the first who, in their extensive epidemiological study of patients admitted to Texas hospitals from 2000 to 2003, marked marijuana abuse as a risk factor for the development of IS. In 2016, Rumalla et al. (2) published a retrospective cohort study in which they analyzed data from a database of hospitalized patients in the USA between 2004 and 2011 and proved the increased likelihood of hospitalization for IS in marijuana smokers by approximately 17%. Hemachandra et al. (3) confirmed in their smaller study an increased risk of IS in marijuana smokers who use it at a frequency of at least once a week while the risk has not been proved in a smaller frequency of abuse.

In our comprehensive stroke center, 26 patients aged 15–44 (so-called "young strokes") were admitted due to IS from January 2016 to June 2017. Three of these patients reported cannabis use at least once a week in their toxicological history.

CASE REPORT 1

28-year-old male reported marijuana usage for 10 years, recently at a dose of 2–3 g of dry matter daily. He was also a tobacco cigarettes smoker (0–20 cigarettes daily). His medical history was insignificant; he did not use any medication. Stroke developed during evening rest during which the patient smoked one joint and experienced palpitation. He developed left side homonymous hemianopsia, mild central left side hemiparesis and left side hemihypoesthesia. There were no focal changes detected on brain computed tomography (CT) performed 90 min after the onset of symptoms. CT angiography (CTA) proved isolated occlusion of right posterior cerebral artery (PCA). He developed a brain infarction in the right occipital lobe with the impact of thalamus (75 × 40 × 35 mm) despite the use of the acute recanalization therapy comprising intravenous thrombolysis with the administration of 65 mg of recombinant tissue plasminogen activator (rtPA; Actilyse®, Boehringer Ingelheim, Ingelheim am Rhein, Germany) performed 145 min after symptoms onset and subsequent mechanical thrombectomy using stent-retriever (Trevo®ProVue™ , Stryker, Fremont, CA, USA) performed 220 min after symptoms onset, during which the thrombembolus was partially removed and P1 and partially P2 segments were recanalized (Fig. 1), and final intra-arterial thrombolysis with the administration of 7 mg of rtPA. Left side homonymous hemianopsia and dysesthesias of the left side extremities and of the left half of the face persisted in neurological findings. The etiology of stroke was not clarified. No arrhythmia was registered both during hospitalization (bed-side monitoring of electrocardiogram [ECG]), nor during a 3-week outpatient Holter-ECG monitoring. There was no proof of cardioembolic source nor right-to-left heart shunt by transesophageal echocardiography (TEE) and a laboratory screening for thrombophilia was negative. Acetylsalicylic acid (Godasal, PRO.MED.CS, Prague, Czech Republic) 100 mg/d was used for a secondary prevention. The patient did not experience any recurrence of neurological problems within a 1.5-year follow-up, while the previous neurological deficit persists.

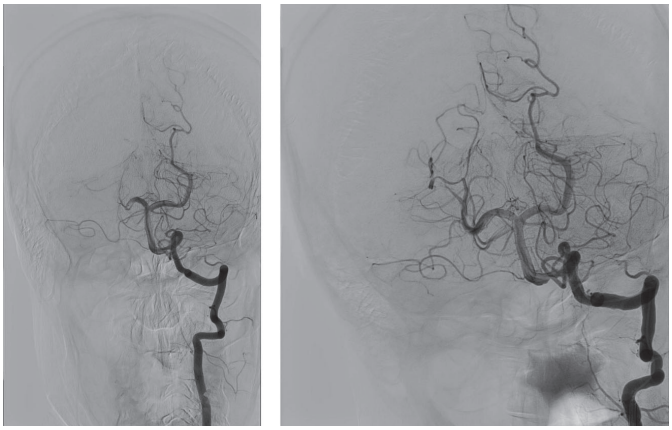

Fig. 1 Digital subtraction angiography: A) occlusion of the right posterior cerebral artery; B) final angiogram after partial recanalization of the P2 segment.

CASE REPORT 2

20-year-old healthy male claimed 6-year abuse of marijuana, in the last 4 years in a dose of 2.5 g of dry matter daily during the admission to our stroke unit. He was also an occasional ecstasy user. He sought a medical examination for 4 days lasting bulbar syndrome, right side neocerebellar syndrome and hypoesthesia of right side limbs. Magnetic resonance imaging (MRI) of the brain detected an acute infarction of the left portion of pons and mesencephalon with a diameter of 10 mm (Fig. 2). Magnetic resonance angiography (MRA) demonstrated occlusion of the central segment of basilar artery, without detection of other pathological changes. Control CTA performed after 6 days showed a stationary finding. During the examination of stroke etiology, there was persistent foramen ovale (PFO) detected on TEE and we noticed recurrent night asymptomatic bradycardia with junction rhythm at heart rate of 35 beats per minute on ECG. Ultrasound ruled out the deep venous thrombosis of the lower limbs. We suspected, that the mechanism of the IS was cardioembolic or paradoxical embolization, and therefore, anticoagulation therapy with warfarin (Orion Corporation Orionintie, Espoo, Finland) 3 mg/d was started and closure of PFO is planned. Eighteen months later, the patient is without a functionally significant deficit, still in the waiting list for the PFO closure.

CASE REPORT 3

28-year-old healthy female reported using marijuana for the last five years at a dose of 1 g of dry matter weekly at the time of admission. Several months ago she stopped smoking tobacco cigarettes. She was without medication at the time of stroke onset, half a year before she ceased using hormonal contraception after 10 years. Firstly, she was admitted to a local department of neurology due to the mild expres-

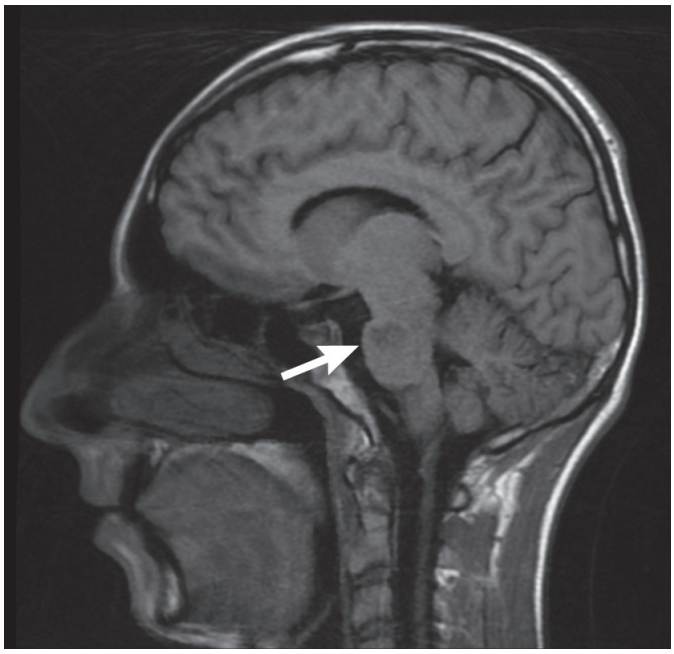

Fig. 2 Magnetic resonance imaging – fluid attenuated inversion recovery, sagittal plane: acute infarction in the pons.

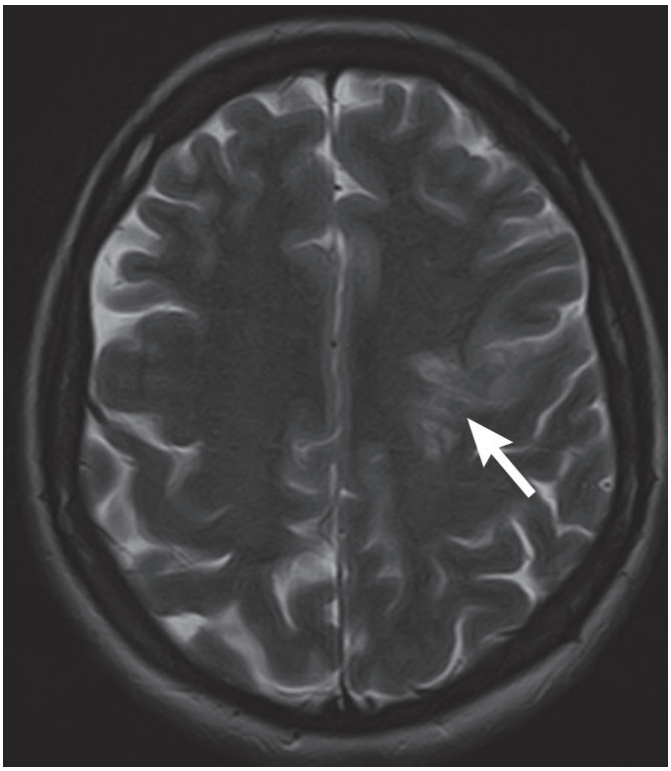

Fig. 3 Magnetic resonance imaging – T2-weighted images, transverse plane: acute infarction in the territory of the left middle cerebral artery.

sive dysphasia and mild right side central hemiparesis with central lesion of the right facial nerve lasting for 3 days and corresponding with the finding of cerebral infarction (2 cm in diameter) in the left frontoparietal region on admission CT. The expressive dysphasia progressed during the hospitalization, brain MRI performed three days later detected multiple ischemic lesions in the territory of the left middle

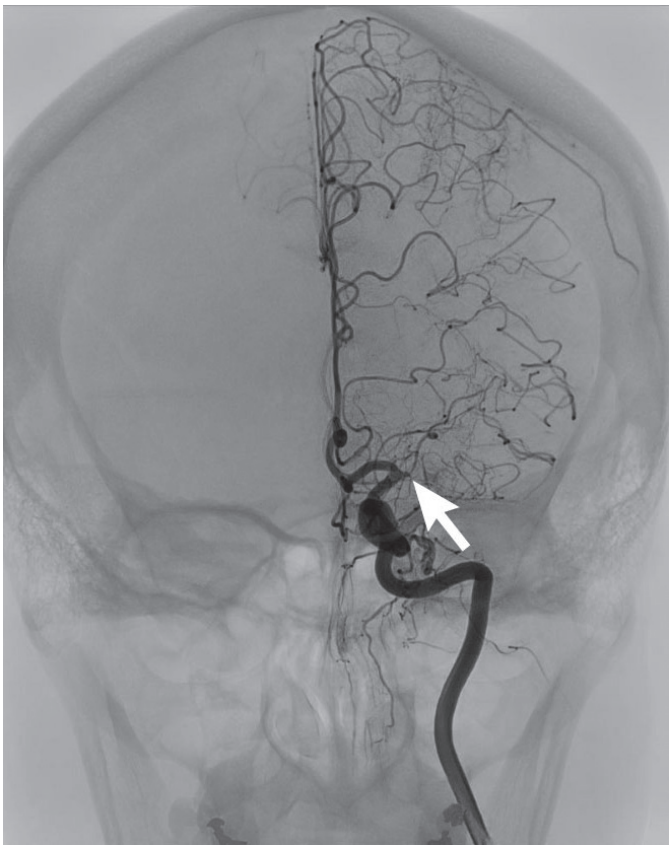

Fig. 4 Digital subtraction angiography: occlusion of the left middle cerebral artery.

cerebral artery (MCA) (Fig. 3) due to the occlusion of its M1 segment detected by MRA.

The patient was later transferred to a comprehensive stroke center, where digital subtraction angiography (DSA) confirmed the occlusion of M1 segment of the left MCA (Fig. 4) and also detected 60–70% stenosis of the intracranial segment of the left internal carotid artery. There was a collateral flow present from the left anterior cerebral artery and left PCA to the unaffected part of the left MCA territory. Well-developed collateral circulation and progression of the neurological deficit suggested a thrombogenic mechanism to the embolic one. One month lasting Holter ECG monitoring and TEE did not prove the source of cardio embolism. Laboratory screening of thrombophilic conditions proved the presence of antiphospholipidic antibodies lupus anticoagulants, APTT-LA index (activated partial tromboplastine time – lupus anticoagulant sensitive reagent) was 3.65 (with a normal ratio of 0.8–1.2). Thus, we consider IS in this patient to be a manifestation of antiphospholipid syndrome. The patient was treated with clopidogrel (Trombex, Zentiva, Prague, Czech Republic) 75 mg/d. During the following year, there was no IS reoccurrence. However, worse speech fluence persisted.

DISCUSSION

Pathophysiological mechanism of marijuana, which contributes to the development of cerebral ischemia, has not been clearly proved. The following mechanisms come to

consideration: 1) cardio embolization during atrial fibrillation (AF), 2) systemic arterial hypotension, 3) reversible cerebral vasoconstriction syndrome (RCVS), and 4) less frequently vasculitis.

Marijuana usage leads to adrenergic stimulation causing the shortening of action potential of myocardium and changing its electrophysiological properties. It may lead to AF (4). Besides that, several hours following the cannabinoid application the risk of myocardial infarction increases five times (5) and this possible atrial myocardial ischemia may also contribute to the development of AF (4).

Acute marijuana use leads to tachycardia which persists for 2–3 h. Repeated exposure to marijuana leads to a gradual weakening of this effect and on the contrary leads to bradycardia. Mechanism leading to bradycardia, which has been proved on animal models, is a blockade of receptors on presynaptic endings of postganglionic fibers of the sympathetic nervous system which leads to the inhibition of sympathomimetic activity and systemic hypotension (6). We suspect a typical interterritorial localization of ischemia in the case of IS caused by systemic hypotension.

RCVS is a clinical-radiological syndrome characterized by a sudden development of a strong headache and multifocal segmental vasoconstriction of cerebral arteries. Headache can occur in an isolated episode or can reoccur within a period of 1–4 weeks. Most often it can be bilateral and may be accompanied by nausea, vomiting, photophobia and confusion (7), in some cases there is also focal neurological deficit present (8). IS belongs among other RCVS complication (8). Basic pathogenetic mechanism of RCVS is most probably defect of cerebrovascular pressure control in increased sympathomimetic reactivity, oxidative stress and endothelial dysfunction (9) may represent a significant role in pathogenesis. RCVS may be idiopathic, however, in 25–60% its occurrence is secondary (9) most often due to usage of cannabinoids or of other vasoactive substances (7). A typical finding in RCVS on CTA, MRA or DSA of cerebral arteries is a multifocal segmental arterial vasoconstriction. In most RCVS cases, correction of clinical symptoms and vasospasms occurs within 3 months (7).

As a possible cause of a higher risk of IS in marijuana smokers, toxic or autoimmune vasculitis is also less often considered in the literature. Since the 1960s, lower limbs arteritis in cannabinoid users, often leading to gangrene and amputation, has been described. However, the association of cannabinoid abuse with vasculitis of the central nervous system has not yet been described.

In our presented case reports we admit causal association between marijuana abuse and IS only in the two cases. Out of four discussed pathophysiological mechanisms related to a cannabinoid abuse, we consider in case reports 1 and 2 exclusively the cardioembolic etiology. The reason for this is the finding of the occlusion of a large cerebral artery and the absence of cerebral vessels stenosis. The possibility of cardioembolic etiology in case 1 is indirectly supported by the history of palpitation. In the second case, the finding of PFO points at a possible paradoxical embolization which would not be related to the marijuana abuse. Regarding the high PFO incidence, estimated at 34% in the age category of our patient (10), and the absence of deep venous thrombosis, we consider in our second case paradoxical embolization as a probable but not a certain etiological mechanism of IS.

CONCLUSIONS

Cannabinoid use may cause IS, especially in the younger age category. Therefore, in these patients we recommend focusing on the history of cannabinoid abuse and carry out toxicological urine tests. In marijuana chronic users, tetrahydrocannabinol can be detected in the urine for a period of 24 days after the last exposure (11).

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