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CLINICAL CASE REPORT

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Transient Global Amnesia After Cerebral Angiography With Iomeprol

A Case Report

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Abstract: Transient global amnesia is now considered a very rare complication of cerebral angiography. Various etiological mechanisms have been suggested to account for this complication, but no consensus has been reached yet. This case report documents one of the few reported cases of cerebral angiography-related transient global amnesia associated with magnetic resonance imaging (MRI) evidence of unilateral hippocampal ischemia, most probably as a consequence of a transient reduction in regional hippocampal blood flow. However, the possibility of a direct neurotoxic effect of the nonionic contrast media Iomeprol on the Cornu ammonis – field 1 neurons cannot be firmly ruled out.

We describe the case of a 54-year-old woman admitted to our department for left upper limb weakness with acute onset 8 days before. The brain computed tomography (CT) scan performed at admission revealed subacute ischemic lesions in the right watershed superficial territories and a right thalamic lacunar infarct. Diagnostic digital subtraction cerebral angiography was performed 4 days after admission with the nonionic contrast media Iomeprol. A few minutes after completion of the procedure, the patient developed symptoms suggestive for transient global amnesia. The brain MRI performed 22 hours after the onset of symptoms demonstrated increased signal within the lateral part of the right hippocampus on the diffusion-weighted imaging (DWI) sequences, associated with a corresponding reduction in the apparent diffusion coefficient (ADC) and increased signal on the fluid-attenuated inversion recovery (FLAIR) sequences, consistent with acute hippocampal ischemia and several T2/FLAIR hyperintensities in the right watershed superficial territories and in the right thalamus, corresponding to the lesions already identified on the CT scan performed at admission. A follow-up MRI, performed 2 months later, demonstrated the disappearance of the increased signal within the right hippocampus on the DWI, T2/FLAIR, and ADC sequences.

The precise mechanism of transient global amnesia related to cerebral angiography is still unclear, and further studies aimed to determine the definite pathophysiology of this syndrome and consequently to establish specific preventive measures are needed. Although the condition itself is considered to be self-limited, the long-term prognosis and the risk of recurrence in the cases where subsequent angiographic procedures are performed are not established yet.

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Abbreviations: ACA = anterior cerebral artery, ADC = apparent diffusion coefficient, ATP = adenosine triphosphate, CA-1 = cornu ammonis – field 1, CT = computed tomography, DWI = diffusion-weighted imaging, FLAIR = fluid-attenuated inversion recovery, MCA = middle cerebral artery, MRI = magnetic resonance imaging, PCA = posterior cerebral artery, TGA = transient global amnesia.

INTRODUCTION

Cerebral angiography was used for the first time for diagnostic purposes in 1927 by the Portuguese neurologist António de Egas Moniz.[1] In the next 40 years, the technique of catheter angiography for imaging cerebral arteries gradually improved, and its use became widespread in the late 1970s. Despite the continuous development of the technical procedure over the following decades and the use of nonionic contrast media, which significantly improved the safety and comfort of this imaging technique, certain associated neurologic complications, most commonly ischemic events, are still reported. Very rare complications of the technique include transient global amnesia (TGA) and cortical dysfunction.[2]

We describe the case of a patient experiencing TGA after cerebral digital subtraction angiography performed with the nonionic contrast media Iomeprol.

CASE REPORT

A 54-year-old right-handed woman was admitted in our department for left upper limb weakness with acute onset 8 days before. She had a past medical history of hypertension and dyslipidemia, and was currently treated with a statin and an angiotensin-converting enzyme inhibitor. Neurological examination revealed moderate weakness of the left upper limb, numbness and impairment of light touch on the left upper limb, and Babinski sign on the left side. She was alert and fully oriented. Serial-seven recitation, calculations, naming, reading, and writing abilities were normal. Verbal memory recall was normal, both immediately and after 5 minutes.

The brain computed tomography (CT) scan performed at admission (Figure 1) revealed a subacute ischemic stroke in the right middle cerebral artery (MCA)—posterior cerebral artery (PCA) watershed territory, 2 hypodense lesions in the right

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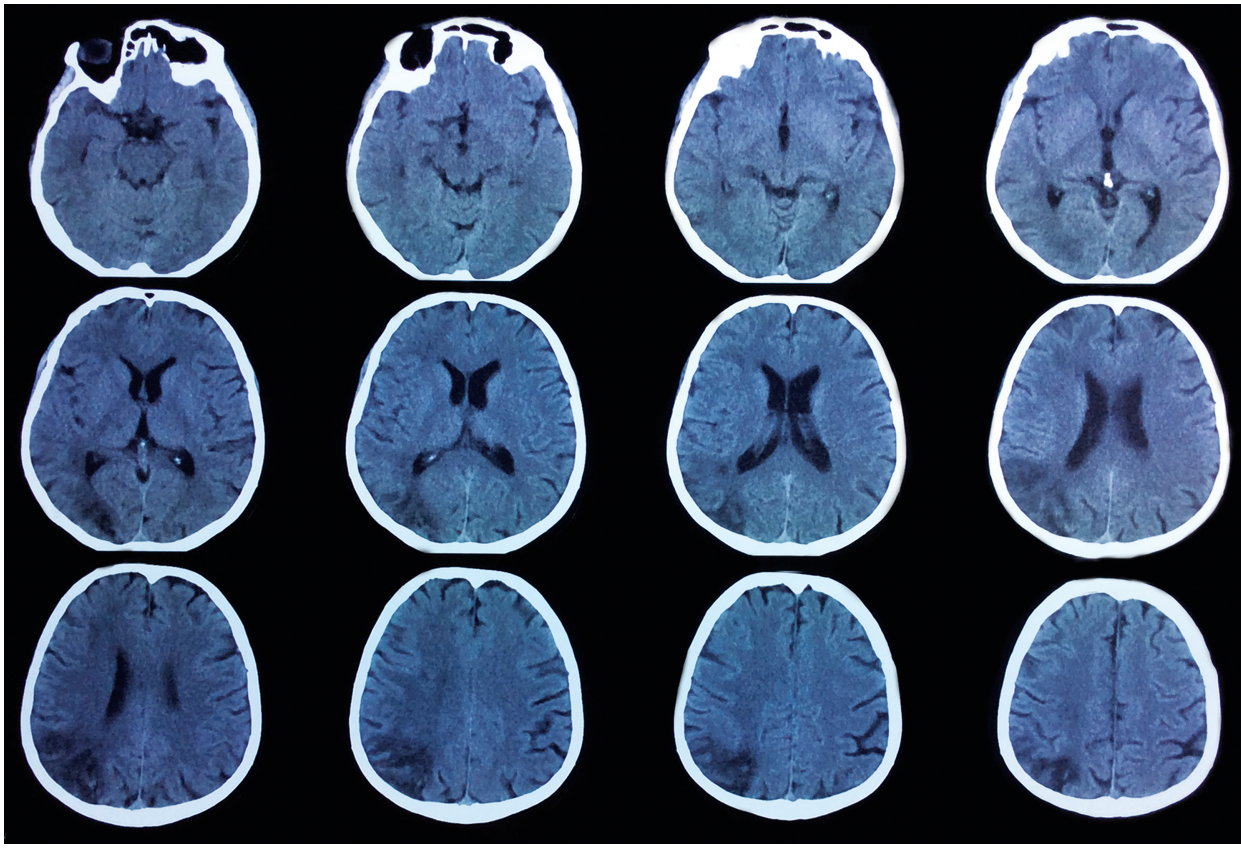

FIGURE 1. Brain CT scan revealing subacute ischemic strokes in the right MCA–PCA watershed territory and ACA territory, and a right thalamic lacunar infarct. ACA = anterior cerebral artery, CT = computed tomography, MCA = middle cerebral artery, PCA = posterior cerebral artery.

anterior cerebral artery (ACA) territory suggestive for subacute ischemic strokes and a right thalamic lacunar infarct. Doppler ultrasound of the cervical and cerebral arteries showed 90% stenosis of the right internal carotid artery and stenosis of the right ACA.

Four days after admission, the patient underwent diagnostic digital subtraction cerebral angiography via a right femoral approach, performed under local anesthesia (Figure 2). The total duration of the procedure was 20 minutes. The contrast media used was 100 mL Iomeprol (Iomeron 300, Bracco Imaging SpA, Milan, Italy). Contrast media injection in the brachiocephalic trunk revealed 85% right internal carotid artery stenosis without intracerebral filling of the ACA. Study of the left common carotid artery showed normal aspect of the left internal carotid artery with normal intracerebral filling of the ipsilateral arteries and of the right ACA. Both vertebral arteries had normal angiographic appearance.

A few minutes after completion of the procedure, we observed that the patient was unable to remember anything from the time of her admission to hospital and asked repeated questions. A detailed neurological examination revealed that the patient was not oriented in location and time, but oriented in personal data. She did not know the reason of hospitalization or how or when she had been transported to the hospital. She was unable to acquire and retain new memories, and repeated the same questions regarding her location and her illness over and over again. She could state her address and the names of the family members, but could not recall her activity during the past week. The remaining neurological examination was otherwise similar to the one performed at admission.

Over the next hours, the anterograde amnesia gradually improved till complete remission. Twenty-four hours after the angiography, she still had mild retrograde amnesia and she could not remember the events of the preceding day, including the time passed in the angiography room. During the following days, the retrograde memory disturbance gradually improved and neurological examination performed 7 days after the angiography revealed a memory gap of the day when the angiography was performed without other significant memory problems.

A brain magnetic resonance imaging (MRI) was performed 22 hours after the cerebral angiography (Figure 3), demonstrating increased signal within the lateral part of the right hippocampus on the diffusion-weighted sequences associated with a corresponding reduction in the apparent diffusion coefficient (ADC) and increased signal on the fluid-attenuated inversion recovery (FLAIR) sequences, consistent with acute hippocampal ischemia. It also revealed several T2/FLAIR hyperintensities with decreased ADC in the right watershed superficial territories and in the right thalamus, corresponding to the lesions already identified on the brain CT scan performed at admission.

Repeated brain MRI 7 days after the angiography showed a decrease of the diffusion-weighted imaging (DWI) signal intensity within the right hippocampus, with persistence of the increased signal on the FLAIR and T2 sequences, and the

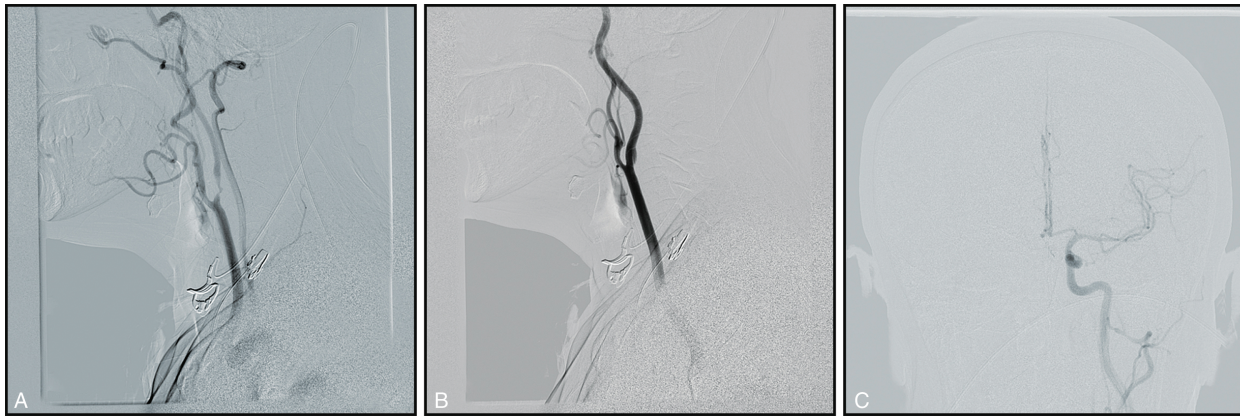

FIGURE 2. Digital subtraction cerebral angiography showing (A) 85% right internal carotid artery stenosis, (B) normal aspect of the left internal carotid artery, and (C) intracerebral filling of the right anterior cerebral artery after contrast media injection in the left internal carotid artery.

same aspect of the other previously described lesions (Figure 4).

At follow-up, 2 months after the angiography, the memory gap of the angiography day persisted, without other significant memory disturbances. The MRI performed 2 months after the angiography (Figure 5) demonstrated the disappearance of the increased signal within the right hippocampus on the diffusion-weighted, T2/FLAIR, and ADC sequences.

DISCUSSION

Cerebral angiography is an invasive procedure associated with relatively low but potentially severe complication rates. Neurologic events are reported to occur in approximately 1.3% to 2.6% of the examinations. Factors associated with an increased risk of neurological complications include the indication for angiography of subarachnoid hemorrhage, atherosclerotic cerebrovascular disease and arteriovenous malformations, history of cardiovascular disease, fluoroscopic time longer than 10 minutes, and advanced patient age.[3,4] In a retrospective analysis of 19,826 angiographic procedures, transient ischemic attacks accounted for 2.09% of the neurologic complications, reversible ischemic neurologic deficits for 0.36%, and established stroke for 0.14%.[3] Several causes and mechanisms have been proposed to account for the neurological complications arising after cerebral angiography. These include mechanical detachment of arterial wall plaques by the catheter with distal embolization, arterial dissections, clot formation around the catheter and the guide wire, platelet activation, changes in red

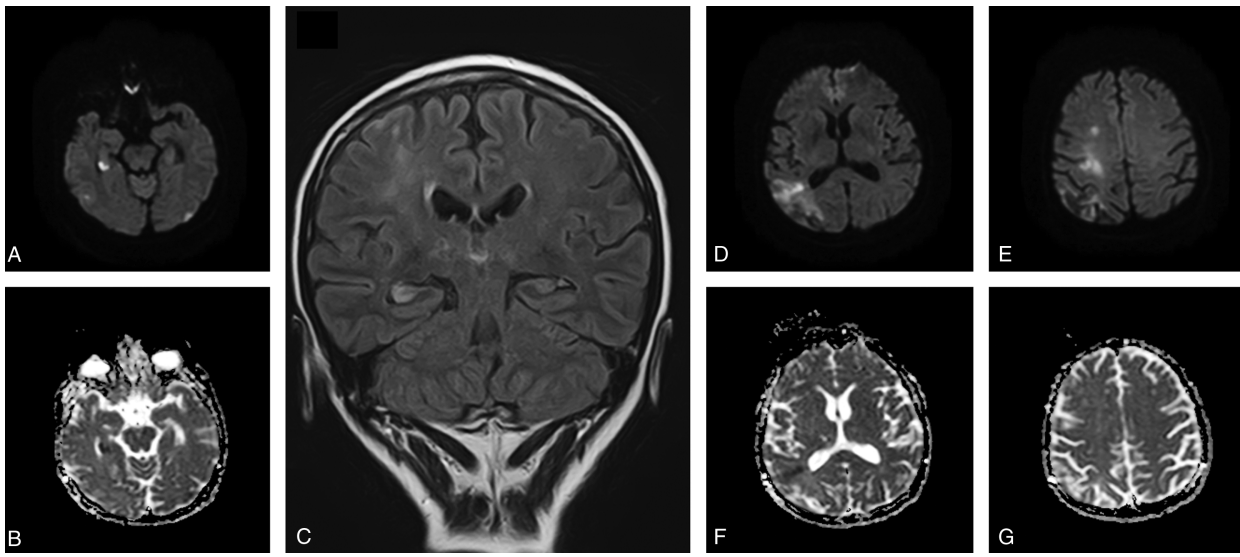

FIGURE 3. Brain MRI performed 22 hours after the cerebral angiography demonstrating (A) increased signal within the lateral part of the right hippocampus on the DWI sequences and (B) corresponding reduction in the ADC and (C) increased signal on the FLAIR sequences, consistent with acute hippocampal ischemia, (D, E) increased DWI signal with (F, G) decreased ADC in the right watershed superficial territories and in the right thalamus (confirming the acute ischemic lesions identified on brain CT at admission). ADC = apparent diffusion coefficient, CT = computed tomography, DWI = diffusion-weighted imaging, FLAIR = fluid-attenuated inversion recovery, MRI = magnetic resonance imaging.

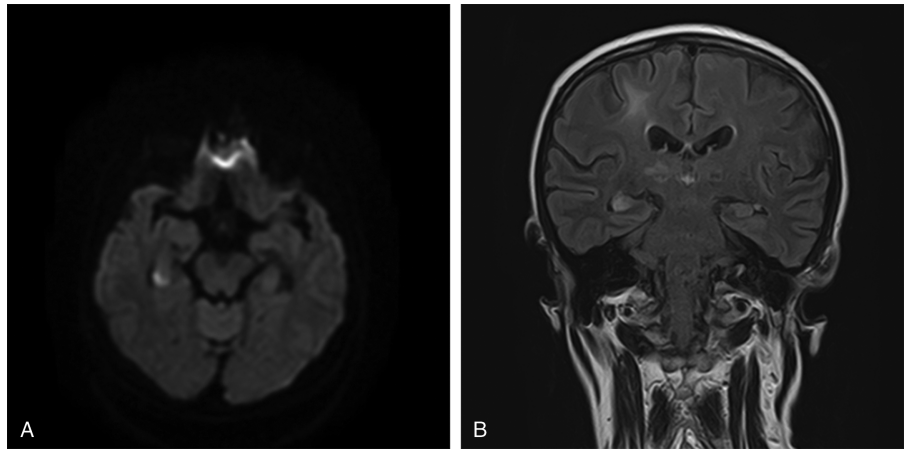

FIGURE 4. Brain MRI performed 7 days after the angiography showing (A) a decrease of the DWI signal intensity within the right hippocampus with (B) persistence of the increased signal on the FLAIR sequences. DWI = diffusion-weighted imaging, FLAIR = fluid-attenuated inversion recovery, MRI = magnetic resonance imaging.

cell morphology, and blood viscosity and direct neurotoxic effect of contrast material.[5]

Transient global amnesia is now considered a very rare complication of cerebral angiography occurring in approximately 0.2% of the examinations performed with nonionic contrast media.[4] The first case of TGA after cerebral angiography was reported in 1981 by Wales and Nov.[6] During the following years, isolated cases and a number of series have been reported.[7–10] With the herald of nonionic contrast media, the rate of complications associated with cerebral angiography diminished and accordingly the number of reported cases of angiography related TGA decreased. The first case of TGA after the use of nonionic contrast media has been reported in 1989 by Giang and Kido,[11] and since then other 17 cases have been reported.[12–20]

More than 50 years after its initial description by Fisher and Adams,[21] TGA remains one of the most surprising syndromes in clinical neurology. According to the diagnostic criteria proposed by Caplan[22] and later reviewed by Hodges and Warlaw,[23,24] TGA is a clinical syndrome characterized by sudden onset of anterograde amnesia, accompanied by repetitive questioning, with or without retrograde amnesia, lasting up to 24 hours, without compromise of other neurologic functions.[25] Although the core amnestic syndrome usually lasts less than 24 hours, mild neuropsychological deficits can last for days after the episode.[26,27]

Our patient fulfilled the criteria for TGA, with complete resolution of the anterograde memory dysfunction during the first 24 hours, but the impairment of retrograde memory lasted longer and gradually improved over 1 week. Several cases reported in the literature show the same pattern of memory recovery and even longer retrograde memory deficits,[28,29] so we consider this clinical picture suggestive for transient global amnesia.

Various etiological and pathophysiological mechanisms have been suggested to be associated with nonangiographic-related TGA, including migraine-related mechanisms, hypoxic-ischaemic events, venous flow abnormalities, epileptic phenomena, and psychological disturbances, but yet, no consensus about the cause of this syndrome has emerged from any of these theories.[30] For a long time, the leading hypothesis was that TGA was caused by abnormal cerebral venous drainage

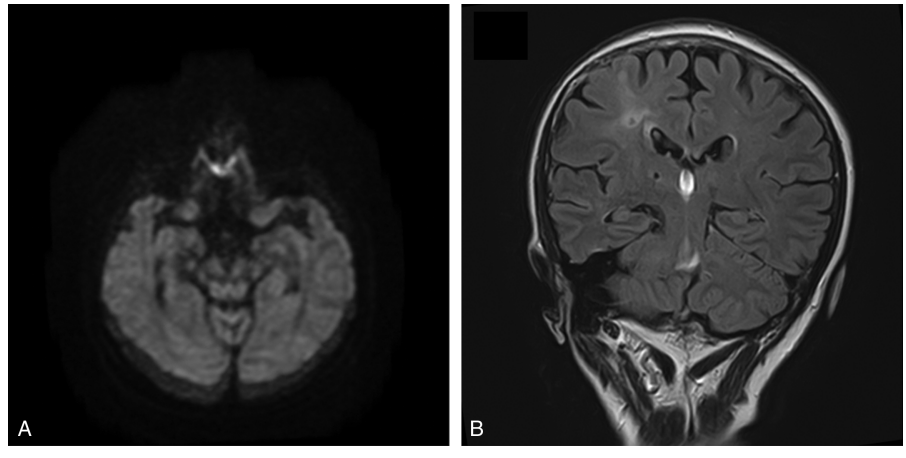

FIGURE 5. Brain MRI performed 2 months after the angiography demonstrating disappearance of the increased signal within the right hippocampus on the (A) DWI and (B) FLAIR sequences. DWI = diffusion-weighted imaging, FLAIR = fluid-attenuated inversion recovery.

from the temporal lobes, due to internal jugular vein valve incompetence, with subsequent venous congestion and ischemia of the mesiotemporal region.[31] However, studies combining ultrasonography and magnetic resonance venography in patients with TGA failed to show a direct association between jugular flow and this amnestic syndrome.[32]

Recent neuropsychological and MRI studies of the brain suggest a transient functional and structural dysfunction of the Cornu ammonis – field 1 (CA-1) sector of the hippocampal cornu ammonis in TGA patients.[26] The neurons located in this area show a selective vulnerability to cellular metabolic stress (such as during hypoxemia and ischemia) that leads to glutamate and calcium-induced and apoptosis-mediated ''delayed neuronal death'' of the affected neurons during the first 72 hours after hypoxic insult.[26] Several theories have been proposed to explain the susceptibility of hippocampal CA-1 neurons to metabolic stress and delayed neuronal death, such as glutamate excitotoxicity, prolonged inhibition of protein synthesis, disturbed heat-shock protein expression, alteration of the lipid metabolism and generation of free radicals, dysfunction of the energy metabolism and regional blood flow, and induced apoptosis.[33] Abe et al[33] summarized these theories and proposed the mitochondrial hypothesis. According to this concept, a quantitative lack in adenosine triphosphate (ATP) in the hippocampal CA-1 neurons would lead to intracellular motor protein dysfunction, alteration of the mitochondrial shuttle system, and progressive energy failure of the cell resulting in ischemic delayed neuronal cell death.[33]

In which way could cerebral angiography promote any of these alterations in the CA-1 neurons still remains a matter of debate. In patients with TGA related to cerebral angiography, postulated mechanisms for this syndrome include ischemia (from atherosclerotic plaque, catheter tip, contrast particulate embolus, or vasospasm) or direct neurotoxic effects of the contrast media.[13,15]

The particular anatomical arrangement of the hippocampal arteries may predispose the Sommer sector to ischemia during cerebral angiography. The blood supply of the hippocampus is provided by multiple collateral branches of the PCA and anterior choroidal artery. These branches form a network of superficial hippocampal arteries that in turn give rise to the deep intrahippocampal arteries located intraparenchymally. Two arcades of deep hippocampal arteries form a watershed zone at the level of CA-1 subfield.[34,35] It can be hypothesized that the high metabolic activity of hippocampal CA-1 neurons,[33] coupled with a reduction in regional cerebral blood flow during cerebral angiography, may promote the appearance of transient global amnesia as a complication of this procedure.

Several authors have favored a direct neurotoxic effect of the contrast media as the causative factor leading to transient global amnesia after cerebral angiography.[9,11,12] This complication has been observed with both ionic and nonionic contrast agents, being reported 3 times as prevalent using the former.[20] Due to their hyperosmolality, contrast agents are considered to have neurotoxic effects by temporarily disrupting the blood–brain barrier with subsequent parenchymal penetration.[36] It is hypothesized that hypertonic solutions draw water out of the endothelial cells of brain vessels, causing shrinkage of these cells, which leads to separation of the tight junctions.[37] However, neurotoxicity of contrast agents cannot be attributed only to their osmolality, but also to their viscosity, chemical features, and ionic characteristics.[38,39] The risk of neurotoxic effects after intra-arterial administration of the contrast media is exacerbated when the blood–brain barrier is already damaged.[38] Our patient suffered an ischemic stroke several days before the cerebral angiography was performed, so a pre-existing disruption of the blood–brain barrier could be a reasonable possibility. Even if Iomeprol is a nonionic, monomeric iodinated contrast medium with lower osmolality and viscosity, and higher water solubility as compared with other nonionic contrast agents,[40] being currently considered one of the contrast agents with the lowest risk of neurotoxicity,[38] we cannot rule out a direct toxic effect of the contrast agent on the hippocampal CA-1 neurons leading to transient global amnesia in our patient.

Some authors have advocated that arterial spasm is the most likely mechanism of individual cases of transient global amnesia after cerebral angiography.[13,16] In our case, the MRI performed 22 hours after the angiography demonstrated acute hippocampal ischemia of the right hippocampus. We consider that the occurrence of arterial vasospasm affecting only the branches of the PCA or of the anterior choroidal artery that vascularize the hippocampus is unlikely.

Structural MRI imaging supports the central role of the hippocampal CA-1 neurons in the pathophysiology of TGA. Recent studies that used high-resolution MRI have shown that focal hyperintense lesions correlating to restricted diffusion within the CA-1 sector of the hippocampal cornu ammonis can be reliably detected in patients with TGA.[26] The identification of hippocampal lesions is dependent on the time of imaging. The maximum level of detection by the use of DWI occurs within 48 to 72 hours after onset of symptoms, and lesions can be detected for up to 7 to 10 days after the onset of TGA.[41,42] Correspondingly, ADC values have minimum values between 24 and 72 hours, and normalize after 10 days.[41] This temporal profile could be explained by the DWI findings in reversible cerebral ischemia studies that follow a biphasic pattern, with high detectability during the acute ischemic period, low detectability in the 12 hours after the ischemic period, and a second raise in detectability to a maximum between 3 and 7 days after the reversible ischemic insult. Why this pattern exists remains unclear, but it is appealing to ascribe it to delayed neuronal death, due to energy failure induced by mitochondrial damage.[43] In a study on 41 patients with TGA, follow-up MRI performed at 4 to 6 months after the onset of the index episode of transient global amnesia did not show transition of the DWI/T2 lesion into residual cavities or signal changes corresponding to evolving gliosis.[26]

The MRI performed in our patient 22 hours after the cerebral angiography showed increased signal within the lateral part of the right hippocampus on the diffusion-weighted and FLAIR sequences associated with a corresponding reduction in the ADC. The 2 follow-up MRI examinations, performed 7 days and 2 months later, showed a decrease of the DWI signal intensity within the right hippocampus, with persistence of the increased signal on the T2/FLAIR sequences and, respectively, complete disappearance of the increased signal within the right hippocampus on the diffusion-weighted and T2/FLAIR and ADC sequences. This temporal profile of the signal changes on MRI imaging of our patient is consistent with the findings of the studies mentioned above.

CONCLUSIONS

The precise mechanism of TGA related to cerebral angiography is still unclear and further studies aimed to determine the definite pathophysiology of this syndrome and consequently to establish specific preventive measures are needed. Although TGA is a very rare complication of this procedure, clinicians

and radiologists should be aware of its possible occurrence and carefully monitor the patients with symptoms suggestive of TGA by neurological examination and brain MRI. Although the condition itself is considered to be self-limited, the long-term prognosis and the risk of recurrence in the cases where subsequent angiographic procedures are performed are not established yet.

To our knowledge, the case described is one of the few reported cases of cerebral angiography-related TGA associated with MRI evidence of unilateral hippocampal ischemia, most probably as a consequence of a transient reduction in regional hippocampal blood flow. However, we cannot firmly rule out the possibility of a direct neurotoxic effect of the nonionic contrast media Iomeprol on the hippocampal CA-1 neurons.

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