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Case Report

Vasogenic Edema of the Basal Ganglia after Intra-Arterial Administration of Nimodipine for Treatment of Vasospasm

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The intra-arterial administration of nimodipine (IAN) is commonly used for cerebral vasospasm refractory to medical treatments. We report two cases of vasogenic edema after IAN. Our patients with aneurismal subarachnoid hemorrhage presented with vasospasm, which was treated by IAN. Consequently, vasogenic edema developed in the basal ganglia. Reperfusion following IAN for vasospasm may have the potential for inciting vasogenic edema in the ischemic brain.

Key Words : Brain edema · Chemical angioplasty · Nimodipine · Vasospasm.

INTRODUCTION

Vasospasm is a well-recognized complication of a ruptured aneurysm and is the leading cause of significant morbidity and mortality after subarachnoid hemorrhage (SAH)[6]. The timely application of endovascular procedures, including balloon angioplasty and intra-arterial infusion of vasodilating agents, is effective at reducing the vasospasm intractable to medical treatment. Intra-arterial infusion of nimodipine (IAN) has been regarded as safe and well tolerated in patients with cerebral vasospasm after SAH[5,10]. Transient hypotension and bradycardia are the only reported adverse effects of IAN. We describe two cases of vasogenic edema in the basal ganglia after IAN for treatment of SAH-induced vasospasm.

CASE REPORT

Case 1

A 40-year-old woman developed two episodes of sudden headache, at an interval of two weeks and consequently underwent magnetic resonance imaging (MRI) of the brain at an outside clinic. The woman patient was diagnosed with spontaneous SAH and was referred to our stroke center. Upon admission, she was alert and had no neurological deficits. Cerebral angiography revealed a saccular aneurysm at the bifurcation of the right middle cerebral artery (MCA) and also revealed diffuse vasospasm of the right MCA and anterior cerebral artery (ACA) (Fig. 1A). Endovascular coil embolization of the aneurysm was planned. Chemical angioplasty for relief of vasospasm was performed prior to coil embolization. As per our hospital's protocol for performing a chemical angioplasty, 2 mg of nimodipine was diluted with 30 mL of normal saline to 25%, and manually injected at a rate of 2-4 mL per minute through a guiding catheter into the right internal carotid artery. The aneurysm was then successfully occluded with two detachable coils, while the parent artery was preserved. After packing the aneurysm with coils, 2 mg of nimodipine was injected again into the right MCA through a microcatheter as with the previous IAN. The vasospasm was markedly improved upon final angiography (Fig. 1B). CT scan taken immediately after endovascular procedure showed a mild contrast enhancement hyperattenuation in the basal ganglia. According to our hospital's protocol for the prevention of vasospasms, the administration of intravenous nimodipine at a dose of 2 mg per hour was performed just after endovascular management.

On the second hospital day, the patient became drowsy with left-sided weakness, and consequently underwent an emergent

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brain MRI, including a diffusion-weighted MRI (DWI) and MR angiography. The DWI and the apparent diffusion coefficient (ADC) map demonstrated several small diffusion-restrictive lesions scattered throughout the right MCA territory (cortex of frontal and parietal lobes, and lentiform nucleus) (Fig. 1C, D). T2-weighted imaging revealed high signal lesion at the right basal ganglia, which did not match the lesions depicted on DWI (Fig. 1E). ADC map demonstrated T2 hyperintense lesion had high ADC value. MR angiography showed significant stenosis of the right MCA and ACA, which was suspected as being a vasospasm. Because the T2 hyperintensive lesion with high ADC value suggests mainly vasogenic edema, we thought that this case should be included in the indication of the endovascular management of vasospasms. An emergent cerebral angiography showed severe vasospasm of the right MCA and ACA. A 3 mg of nimodipine diluted with 45 mL of normal saline was infused through a microcatheter placed at the origin of the MCA and ACA. With the vasospasm almost resolved, there were no significant systemic side-effects, such as hypotension or bradycardia, noted during IAN. Immediately after IAN, brain CT showed a contrast enhancement in the basal ganglia. Although basal ganglia edema was constantly indicated on the CT scans after performing the procedure, the patient became alert again within the next 24 hours. Transcranial Doppler (TCD) sonography examinations were performed on alternate days and the TCD velocities of the right MCA did not exceed 120 cm/s. The brain CT acquired on the 6th hospital day showed the increase of the extent of cerebral oedema (Fig. 1F). However, the patient presented as only a headache and mild upper extremity weakness (grade 4). This discrepancy between the clinical symptoms and parenchymal lesion on the brain CT and TCD result was far from matching the finding of the cerebral infarction induced by vasospasm. On the 7th hospital day, she suddenly presented with drowsiness and left hemiplegia. An emergent brain CT scan showed the progression of the cerebral edema as well as showing a midline shift to the left. A decompressive craniectomy was performed and an immediate postoperative CT angiography revealed no spastic intracranial arteries. We hypothesized that the progression of vasogenic edema induced by IAN was the cause of our patient's deterioration. In spite of the surgical and medical management, the patient's left hemiplegia remained unchanged. She was discharged with a modified Rankin score of 5.

Case 2

A 24-year-old woman presented with a sudden headache and diplopia. A brain CT revealed diffuse SAH in the suprasellar cistern and sylvian fissure. CT angiography showed a saccular aneurysm at the origin of the left anterior choroidal artery. Endovascular obliteration of the aneurysm was achieved using three detachable coils. On the 10th hospital day, the patient became drowsy. An immediate perfusion CT revealed a significant increase in the mean transit time in both ACAs and in the left MCA regions, and any abnormal attenuation was not seen on plain brain CT. An emergent angiography showed moderate to severe vasospasm extending from distal ICA to both ACAs and left MCA (Fig. 2A). A 4 mg infusion of nimodipine diluted with 60 mL of normal saline was manually injected at a rate of 2-4 mL per minute into the left M1 and A1 segments, which resulted in the relief of the vasospasm (Fig. 2B). On the 12th hospital day, a follow-up CT showed multiple low-attenuation lesions in the antero-medial aspects of both frontal lobes and left basal ganglia (Fig. 2C). However, the patient was alert and neurologically intact. She was discharged without neurological deficits.

Three month follow-up brain MRI demonstrated that, although the infarctions persisted in both frontal lobes, the lesion in the lentiform nucleus was completely disappeared (Fig. 2D). We believe that the transient lesion in the left lentiform nucleus may have represented the vasogenic edema induced by IAN, un-

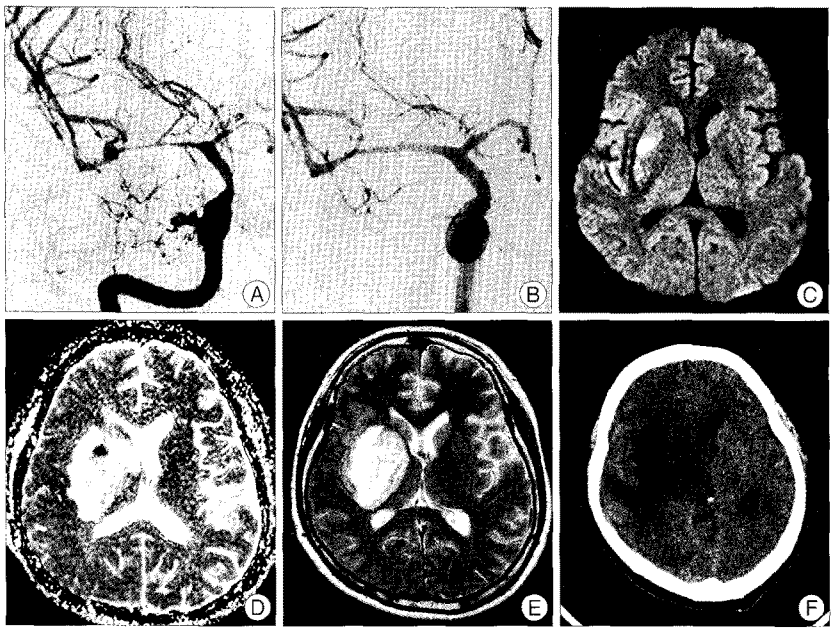

Fig. 1. A 40-year-old woman presented with subarachnid hemorrhage from a ruptured aneurysm. A right internal carotid angiography (A) demonstrates severe vasospasm of the middle cerebral artery (MCA) and a saccular aneurysm at the MCA bifurcation (arrow). The vasospasm was resolved after the intra-arterial infusion of nimodipine. Control angiography (B) after infusion of 4mg of intra-arterial nimodipine shows reduction of vasospasm. One day later, a diffusion-weighted MRI (DWI) (C) and apparent diffusion coefficient map (D) reveals a small, acute ischemic lesion in the right basal ganglia. A T2-weighted MRI (E) shows diffuse vasogenic edema of deep brain structure, which is significantly larger than the hyperintense lesion on DWI. The brain CT acquired on the 6th hospital day (F) shows cerebral edema involving the basal ganglia and deep white matter of the right cerebral hemisphere.

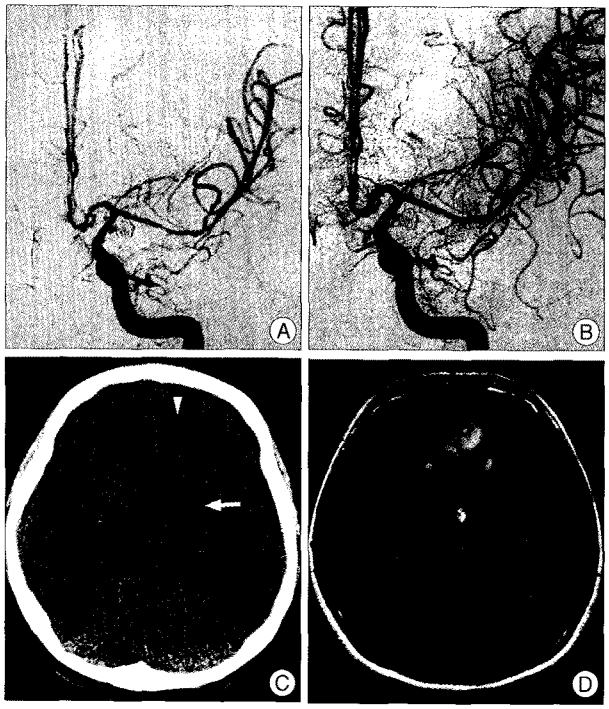

Fig. 2. A 24-year-old woman presented with subarachnoid hemorrhage and a ruptured aneurysm. On 10 days after coil embolization of aneurysm, left internal carotid angiography (A) reveals moderate arterial vasospasm, which is improved after intra-arterial administration of nimodipine (IAN) (B). A brain computed tomography (C) at 2 days after IAN shows low-attenuating lesions in the left globus pallidus and internal capsule (arrow), as well as in the medial aspect of the anterior frontal lobe (arrowhead). On 3-month follow-up fluid attenuation inversion recovery (FLAIR) magnetic resonance image (D), the basal ganglia lesion disappears. Conversely, the lesion in the medial aspect of the anterior frontal lobe is persistent.

like the vasospasm-induced infarctions in both ACA territories.

DISCUSSION

Endovascular treatment of vasospasm is indicated for patients with ischemia that is secondary to vasospasm when appropriate medical therapy has failed. Endovascular treatment of the vasospasm is classified into two categories; a balloon angioplasty of stenotic segments and the chemical relaxation of the vasospasm by the intra-arterial administration of drugs such as papaverine[6]. Although the percutaneous trans-arterial balloon angioplasty has an advantage in that its effect is permanently maintained, it is limited to the proximal vessel segment and it should be performed by an experienced neurointerventionist to avoid potential serious complications. The effect of pharmacologic angioplasty is transient. However, it is suited for distal vessels and diffuse vasospasm and is subject to fewer technical difficulties.

Intra-arterial administration of papaverine had long been accepted as a viable endovascular management for medically intractable vasospasm. However, papaverine had several complications such as increased intracranial pressure and reverse vasospasm. Moreover, the intra-arterial infusion of papaverine appears to be neurotoxic in posterior circulation, and may lead to a disruption of the blood-brain barrier (BBB)[6]. Today, several vasodilating agents instead of papaverine have been tried for intra-arterial administration. Nimodipine, a calcium channel blocker, is one of these vasodilatory drugs that has been widely tried for intra-arterial infusion. Several studies have shown that intra-arterially administered nimodipine is safe and effective for the treatment of cerebral vasospasm. The only complications of IAN reported in previous studies have been transient hypotension and bradycardia[1,5].

Oral and intravenous administration of nimodipine has been shown to promote improvement of regional cerebral blood flow in patients with vasospasm after SAH[3,10]. However, several experimental animal studies have demonstrated that nimodipine may interfere with cerebral autoregulation and also impair the blood-BBB[4,9]. Papaverine which acts directly on vascular smooth muscle also can lead to the opening of the BBB[7]. Autoregulation is provided by the vascular smooth muscles, which contract in the presence of calcium. Calcium antagonists prevent vasospasm by blocking a calcium influx into the vascular smooth muscles and thus promoting muscle paralysis. However, because nimodipine has both negative and positive effects on the integrity of the BBB[2], further study should be pursued to investigate the mechanisms of vasogenic edema after IAN. Reperfusion injury should be considered as another possible cause of the vasogenic edema. Reperfusion injury can be affected either by mechanical angioplasty or thrombolysis. Hyperperfusion resulting in the restoration of cerebral circulation may contribute to the development of reperfusion injury by vasogenic edema or hemorrhage. Breakdown of the BBB during cerebral reperfusion may lead to the vasogenic edema. Some investigations demonstrated a disruption of the BBB after reperfusion of the brain[8].

In our cases, the disturbance of autoregulation induced by nimodipine, combined with reperfusion injury, may result in vasogenic edema in the lenticulostriate artery region. A larger volume of nimodipine would more likely flow into the perforating branches of the proximal M1 segment than into the distal segment of the MCA, because vasospasm would disturb the flow to the distal segment of the MCA.

During the preparation of this manuscript, we found a report that showed the BBB disruption following intra-arterial administration of papaverine[7]. However, to our knowledge, this is the first report of IAN-induced brain edema. The cerebral edema in our first case showed T2 hyperintense lesion in right basal ganglia and corona radiata, which was significantly larger than the diffusion restrictive lesion on DWI. The large T2 hyperintense area with high ADC value within the lesion would result from the vasogenic edema, and was differed from the acute ischemic lesion caused by vasospasm. Despite significant cerebral edema on CT, only mild symptoms were present, and the lesion worsened upon a second IAN. Therefore, the brain lesion would be more likely vasogenic edema rather than ischemic in-

farction. We suggested that the mechanism of the vasogenic edema after IAN would be the opening of BBB by nimodipine and the locally increased cerebral blood flow by vasodilatation. Serial brain CTs in the second case showed reversible changes in the low attenuation lesions of the basal ganglia, unlike the infarction that developed simultaneously in the ACA region. When new CT lesions appear in the basal ganglia after IAN, DWI, or serial, follow-up imaging may be useful in differentiating between vasospasm-induced infarction and vasogenic edema.

Because IAN has the transient effect of causing vasospasm, multiple procedures may be required in patients with persistent vasospasm. Vasogenic edema may be worsened by multiple IAN treatments, as we noted in our first case. Therefore, the accurate diagnosis of vasogenic edema after IAN is important for the proper treatment of patients with vasospasm.

CONCLUSION

IAN has been considered a safe and effective method for reducing vasospasm after SAH. However, in rare cases, locally infused nimodipine may result in vasogenic cerebral edema. IAN-induced edema is difficult to differentiate from vasospasm-induced infarction on conventional brain CT. Therefore, advanced or modified brain imaging techniques such as diffusion-weighted MRI, perfusion-weighted imaging, and serial follow-up CT may be useful in the diagnosis of vasogenic edema after IAN.

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