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Clinical report

Delayed cerebral ischemia after clipping of middle cerebral artery aneurysms

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Background: Delayed cerebral ischemia (DCI) that occurs more than 14 days after clipping of middle cerebral artery (MCA) aneurysms is rare.
Objective: To investigate whether multiple treatments that prevent vasospasms and microthrombosis may achieve a better outcome for DCI.
Method: We present three cases of subarachnoid hemorrhage (SAH) in patients who experienced DCI before and after MCA aneurysmal clipping. Their clinical manifestations, neuroradiological aspects, treatment, and outcomes are presented. Digital subtraction angiograms and computed tomographic angiography were performed to confirm the MCA aneurysms. Aneurysmal clippings were implemented via a pterional approach within 3 days of the onset of SAH. Triple-H therapy was conducted, and nimodipine was administered intravenously. The three patients were released with intact neurological status within 14 days to 17 days of clipping.
Results: The three patients were readmitted within 7 days after discharge because of cerebral ischemia in the corresponding MCA area. Antiplatelet drugs were administered with resolution of clinical symptoms within a few days.
Conclusion: The occurrence of this kind of DCI is rare. The pathogenesis of DCI is unknown and may be complex. Multiple treatments that prevent vasospasms as well as microthrombosis may achieve a better outcome.

Keywords: Aneurysm clipping, delayed cerebral ischemia, micro-thrombosis, middle cerebral artery

Aneurysms of the middle cerebral artery (MCA) account for 18% to 22% of all intracranial aneurysms and are the third most common location for aneurysmal subarachnoid hemorrhage (SAH) [1-3]. The majority of MCA aneurysms are treated with microsurgical clipping within 0 to 3 d. The incidence of cerebral vasospasm and ischemic infarction are reportedly higher on the third day after surgery [4]. However, the occurrence of delayed cerebral ischemia (DCI) more than 14 d postclipping of the MCA aneurysm has rarely been reported. We report three rare cases of this type of DCI, including the clinical manifestations, angiographic aspects, treatment, and follow-up for each patient.

Case reports

Case 1

A 39-year-old male smoker presented with an abrupt onset of a severe headache and loss of consciousness. Neurological examination on admission revealed drowsiness and neck stiffness, but no cranial nerve deficits nor lateralized motor and sensory findings were observed. Computed tomography (CT) showed SAH, Fisher grade 2. The digital subtraction angiograms (DSA) implemented the following day showed a saccular aneurysm of the right MCA (M1) (**Figure 1A**). The patient underwent craniotomy and surgical clipping later that day. Continuous cerebrospinal fluid drainage via a lumbar subarachnoid catheter was implemented before craniotomy. The patient recovered with intact neurological status after clipping. CT on the third day after surgery showed no signs of ischemia (**Figure 1B**). After triple-H therapy (hypervolemia, hypertension, and hemodilution) and intravenous injection of nimodipine, cerebrospinal fluid (CSF) was analyzed three times a week for glucose and protein, and examined by Gram staining. The patient was discharged on the 17th day after surgery, but was readmitted on the 21st day after surgery because of left-side body weakness. CT showed cerebral ischemia in the region of the right basal nuclei

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(**Figure 1C**). Aspirin (100 mg) was administered daily with resolution of clinical symptoms within a few days. The patient was cured and in excellent condition without any neurological deficit after 1 week of treatment in hospital.

Case 2

A 59-year-old woman with a history of hypertension and myocardial ischemia presented with an abrupt lancinating headache with nausea and vomiting. On admission, the neurological status of this patient was initially intact with severe nuchal rigidity. CT showed SAH predominantly in the right lateral cistern, Fisher grade 2. Computed tomographic angiography (CTA) was performed, and bilateral saccular aneurysm of the MCA was found (**Figure 2A**). The aneurysms were clipped via a right pterional approach because rupture of the right MCA aneurysm was considered to be the more likely cause of the SAH. Continuous cerebrospinal fluid drainage via a lumbar subarachnoid catheter was implemented before craniotomy. The patient recovered with intact neurological status after clipping. CT on the third day after the operation demonstrated no signs of ischemia (**Figure 2B**). After triple-H therapy and intravenous nimodipine injection, the CSF was analyzed three times a week for glucose and protein, and was examined by Gram staining. The patient was discharged on the 14th day after surgery and was to undergo treatment for the contralateral MCA aneurysm when she was physically and mentally prepared. However, on the 17th day after the operation, she was suddenly paralysed on her left side. CT demonstrated cerebral ischemia in the region of the right basal nuclei (**Figure 2C**). Sodium ozagrel was administered intravenously at 80 mg daily, and the patient was discharged with severe hemiparesis of the left upper limb and mild hemiparesis of the right lower limb.

Case 3

A 61-year-old woman with a 10-year history of hypertension suddenly developed severe headache, Hunt–Hess grade 2. On admission, CT showed SAH, Fisher grade 3. CTA conducted on the second day after SAH showed saccular aneurysms on the left MCA (**Figure 3A**). The aneurysm was clipped via a left pterional approach. Continuous cerebrospinal fluid drainage via a lumbar subarachnoid catheter was implemented before a craniotomy. The patient recovered with intact neurological status after clipping. CT on the third day after surgery showed some signs of ischemia (**Figure 3B**), but no clinical signs of neurological deterioration were observed. After triple-H therapy and oral nimodipine administration, the patient was discharged on the 16th day after surgery. On the 18th day after surgery, the patient suddenly developed right-sided hemiplegia. CT demonstrated cerebral ischemia in the corresponding region of the left MCA (**Figure 3C**). The patient recovered and was in good condition after 2 weeks of treatment in hospital.

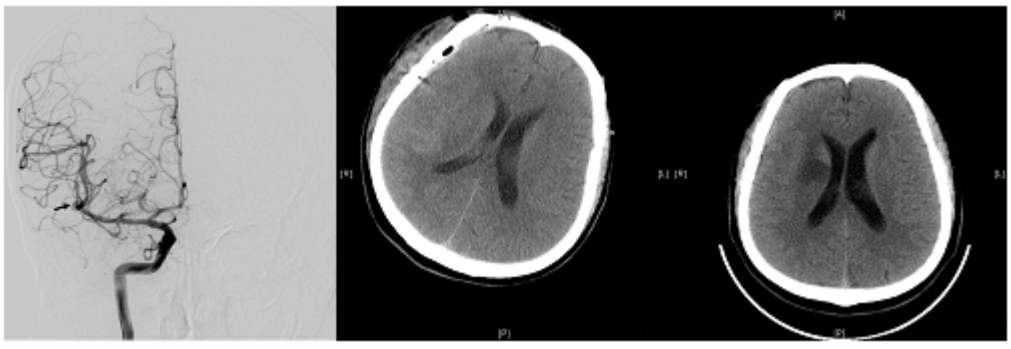

Figure 1. **A**. Right internal carotid artery (ICA) angiography revealing a saccular aneurysm in the middle cerebral artery (arrow). **B**. Computed tomography (CT) on the 3rd day after operation demonstrating no sign of ischemia. **C**. CT demonstrating the cerebral ischemia on the region of the right basal nuclei.

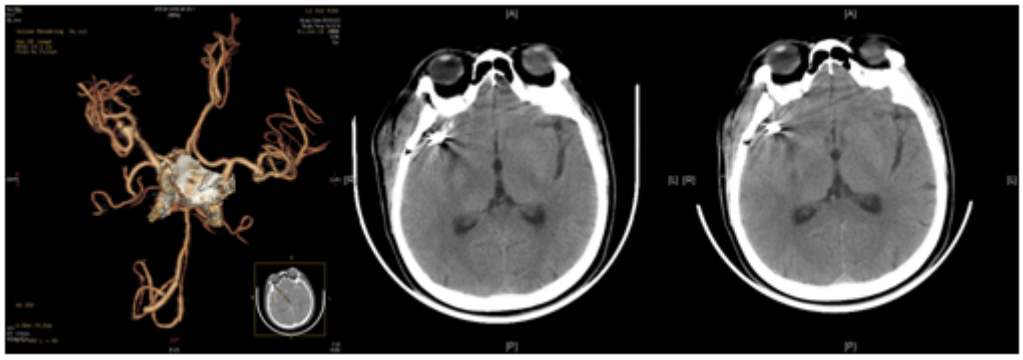

Figure 2. **A**. Computed tomographic angiography (CTA) demonstrating bilateral saccular aneurysms on each side of middle cerebral artery. **B**. Computed tomography (CT) on the third day after surgery demonstrating no sign of ischemia. **C**. CT showing cerebral ischemia in the region of the right basal nuclei.

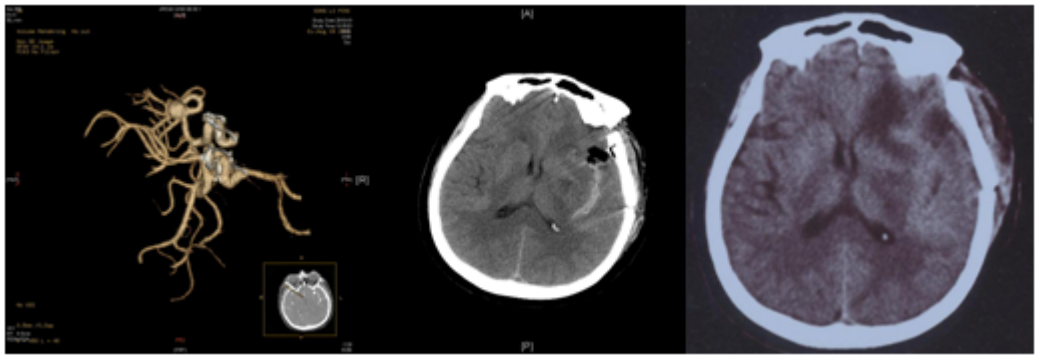

Figure 3. **A**. Computed tomographic angiography (CTA) demonstrating saccular aneurysms on the left side of the middle cerebral artery. **B**) Computed tomography (CT) on the third day after surgery demonstrating suspected signs of ischemia. **C**) CT on the 18th day after surgery demonstrating cerebral ischemia in the region of the left basal nuclei and corona radiate.

Discussion

Delayed vasospasm of large cerebral arteries is an important cause of cerebral ischemia and infarction after SAH [5, 6]. The etiology of cerebral vasospasm remains unclear. Clotting of subarachnoid blood is widely considered as the major etiological factor in vasospasms [7]. The presence of subarachnoid blood may affect the severity and time course of vasospasm, which necessitates its extensive removal to prevent severe delayed ischemic symptoms [8]. Preliminary studies have shown that lumbar drainage markedly diminishes the incidence of CVS and improves the clinical outcome [9-11]. In the cases presented here, the SAH of all three patients initially had good clinical grades (Hunt and Hess Grades 1 to 2). On admission, lumbar puncture was implemented before craniotomy, and subarachnoid continuous drainage was maintained until the 7th day after surgery to evacuate blood clots, achieve brain relaxation, and reduce the risk of hydrocephalus. The CSF was analyzed to identify evidence of inflammation. Triple-H therapy has long been recommended for preventing and treating cerebral vasospasm and stroke (delayed cerebral ischemia) with complex SAH [12], although data confirming the use of triple-H therapy as a prophylactic measure are insufficient [13-15]. In our institution, the triple-H therapy was maintained and nimodipine, a calcium-channel antagonist, was administered until the 14th day after surgery as a prophylactic intervention to prevent the occurrence of cerebral vasospasms. Vasospasms usually occur after the third day, with a high incidence within 5–7 days after hemorrhage and a relatively low risk after the end of the second week (16).

The three patients recovered two weeks after surgery without any neurological deficits and were readmitted to our institution on the 21st, 17th, and 18th day after their respective operations (4, 3, and 2 days after discharge from the hospital, respectively), because they developed hemiplegia. CT demonstrated cerebral ischemia adjacent to the clipped MCA.

These cases represent a different type of DCI from previously reported cases, wherein the DCI happened within 3 days after the operation. For aneurysms treated with microsurgical clipping, vessel strangulation by the clip and decreased vascular diameter are other important causes of cerebral ischemia. The three patients were treated with microsurgical clipping by an experienced cerebrovascular surgical team. CT on the third day after the surgery showed no signs of ischemia, and the three patients were cured within two weeks of surgery without any neurological deficits. No patient showed any further sign of transient ischemic attack. DCI can occur in the absence of cerebral vasospasm [17, 18]. A recent review of the literature indicated that cerebral vasospasm is not the only cause of DCI and that the mechanism of DCI is multifactorial [17]. Microembolisms are an alternative explanation for DCIs beyond 14 days postsurgery in the absence of vasospasms. Transcranial Doppler ultrasound records embolic signals in an alarmingly high number of patients with SAH [19]. Stein et al. examined the brains of 29 patients who died within an average of 8 days after SAH [20]. Thrombi in the small cerebral blood vessels, as detected by immunohistochemical staining for antithrombin III, were common in patients who developed clinical or radiological delayed ischemia. Single cortical infarction near the ruptured aneurysm and multiple infarctions, often including bilateral and subcortical lesions, are the two most frequently observed patterns of delayed cerebral ischemia after aneurysmal SAH [21]. The emerging role of thromboemboli opens the potential for new therapeutic strategies [5, 22]. In our cases, antiplatelet drugs and anticoagulants were administered, and the clinical symptoms disappeared within a few days. This phenomenon indicates that microembolisms rather than vasospasms play a more important role in DCI beyond 14 days after aneurysmal clipping. Vasospasms and microemboli should not be considered as two separate entities, but as complementary entities in the pathogenesis of DCI [23]. The precise etiology of DCI is still not fully elucidated, and more potential therapeutic agents should be developed to obtain better results.

In conclusion, the pathogenesis of DCI more than 14 days after aneurysmal clipping of MCA can be complex and currently unknown. Aside from cerebral spasms, microembolisms may be an important etiology of DCI. Treating the possible vasospasms as well as microthrombosis may achieve better results compared to focussing on one possible pathogenesis alone.

The authors have no conflicts of interest to declare.

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