Case Report
Delayed symptomatic vasospasm after clipping of an unruptured intracranial aneurysm: case report and literature review

Changjiang Ou1, Yili Chen1, Shenghu Wang1, Jun Mo1, Weiwei Hu2

1Department of Neurosurgery, The Fourth Affiliated Hospital of Zhejiang University School of Medicine, Yiwu 322000, Zhejiang, China; 2Department of Neurosurgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou 310009, Zhejiang, China

Received January 23, 2017; Accepted April 14, 2017; Epub June 15, 2017; Published June 30, 2017

Abstract: Symptomatic vasospasm after clipping of unruptured intracranial aneurysms is a rare phenomenon. Herein, a case of delayed symptomatic vasospasm that developed after clipping of a middle cerebral artery aneurysm is reported. The experience in treatment is introduced, and relevant literature is reviewed to investigate the potential pathogenesis. A 50-year-old male was diagnosed with an unruptured aneurysm of the right middle cerebral artery and treated with uneventful clipping under general anesthesia. Motor aphasia and subsequent hemiparesis occurred on the 10th postoperative day. Emergent head computed tomography angiography indicated severe vasospasm of right MCA. The patient was treated with volume expansion, oral nimodipine, and antiplatelet therapy. Recovery at 4 months follow-up as assessed by Glasgow Outcome Scale was IV. The sequelae included moderate weakness in the left hand and mild weakness in the leg. Delayed symptomatic cerebral vasospasm may occur after uneventful clipping of unruptured intracranial aneurysms, causing severe outcomes. Treatments such as volume expansion, vasodilators administration, and intra-arterial angioplasty should be administered to ensure favorable outcomes.

Keywords: Unruptured aneurysm, cerebral vasospasm, clipping

Introduction
Cerebral vasospasm (CVS) with related delayed cerebral infarctions after aneurysmal subarachnoid hemorrhage (SAH), as a major cause of morbidity and mortality after aneurysm obliteration, has since long been widely recognized [1]. Although considered to be mostly correlated with the severity of SAH, CVS has been reported in multiple pathological conditions as traumatic brain injury and brain tumor resection [2-4]. However, Limited number of cases with delayed symptomatic vasospasm after uneventful treatment of unruptured aneurysms have been reported, and little is known about the mechanism.

Herein, we report a patient who developed delayed severe symptomatic vasospasm on the 10th day after clipping of an unruptured right middle cerebral artery aneurysm successfully and uneventfully. The surgical manipulation and mechanical stress commonly result in early vasospasm, whereas the delayed vasospasm occurred in the absence of blood breakdown derivatives, thereby indicating the presence of other factors contributing to the development of vasospasm. The relevant literature was reviewed with emphasis on pathogenesis and treatments of this rare subgroup of patients.

Case report
A 50-year-old right-handed male visited our hospital presenting a mild right temporal headache for half-a-month and denied any sudden episodes of a severe headache or vomiting. Physical examination did not reveal any neck rigidity or other positive signs. A head magnetic resonance imaging (MRI) was performed, which showed an unruptured aneurysm of the right MCA. Digital subtraction angiography (DSA) of
Symptomatic vasospasm with an unruptured aneurysm

the cerebral arteries demonstrated a 6 mm diameter saccular aneurysm located at the upper trunk of right M2 segment, adjacent to the MCA bifurcation (Figure 1A).

A right transpterional approach craniotomy was performed under general anesthesia. The Sylvian fissure could be readily dissected to expose the aneurysm without any sign of previous SAH. The aneurysm was then clipped successfully and uneventfully with two titanium clips without temporary occlusion of the right MCA. Vasospasm was not noted preceding to or associated with the clipping. The patency of the parental artery and the lower trunk of M2 was confirmed to be intact on the intraoperative indocyanine green angiography. The monitoring of both the somatosensory and compound motor evoked potentials was normal during the whole operation process.

On the day of operation, the patient also underwent a regular postoperative computed tomography (CT) scan, which did not show any cerebral or subarachnoid hemorrhage (Figure 1B). The postoperative course was uneventful until one week after surgery when he developed mild to moderate headache on the right side of the head. A subsequent head CT scan did not display any abnormal signs. The headache treated with analgesics showed an improvement, although not completely. On postoperative day 10, a sudden onset of motor aphasia occurred followed by rapidly progressive hemiparesis of the left extremities. The patient was subjected to an emergent head CT and computed tomography angiography (CTA) that indicated excellent clipping of the aneurysm. However, severe vasospasm of both the upper and lower trunks of the M2 segment of the right MCA was observed (Figure 1C). A focal hypoin-
Symptomatic vasospasm with an unruptured aneurysm

tense area in the right frontal lobe and a small amount of epidural hematoma formation on the surgical site were detected on CT (Figure 1D). The patient was treated with volume expansion, oral nimodipine, and antiplatelet therapy (aspirin). MRI was performed 1 week after the onset of aphasia. Persistent vasospasm of the right MCA observed on magnetic resonance angiography (MRA) (Figure 1E), and infarction of MCA-supplied areas of right frontal and temporal lobes on diffusion-weighted imaging (Figure 1F) were present. After 2 weeks of treatments, the patient showed improvements in aphasia but not left hemiparesis. The patient was then transferred to a recovery center for hyperbaric oxygenation treatments and rehabilitation exercises. The Glasgow Outcome Scale (GOS) was IV at 4 months follow-up. Although moderate residual weakness persisted in the left hand, neither his communication nor the walking ability was obliterated.

Discussion

CVS secondary to SAH is a well-known phenomenon. However, the mechanisms are not yet fully comprehended. Thus, the reports of cases with vasospasm after uneventful surgeries for UIAs will expand our understanding of the etiology.

To our knowledge, only 8 cases of unruptured aneurysms which were all treated by clipping have been reported with delayed symptomatic vasospasm [3, 5-8]. Among these, the latency differed, ranging from 5 to 28 days. The other reported cases, wherein the vasospasm symptoms developed immediately or within hours post-surgery were not included in the present study with respect to the plausible mechanical effect on the arterial wall [9-11]. The spasmodic arteriosclerosis were localized or adjacent to the region of aneurysms in all the 9 cases except one [3]. The clinical characteristics of these cases along with our present case were summarized in Table 1.

The incidence rate of CVS after treatments of UIAs is unknown due to the limited number of reported cases, and insufficient attention has been attracted. The largest study of postoperative vasospasm of UIAs was reported by Kitazawa et al. in 2005 [7]. In the retrospective study, 30 patients with paracclinoid aneurysms received microsurgical clipping surgery, 9 patients (30%) developed delayed vasospasm, of which 3 patients (10%) were symptomatic. Other studies are reports of rare cases. However, as angiography is routinely performed postoperatively, the delayed CVS for UIAs, whether symptomatic or not, would be more widely detected.

Nevertheless, the risk factors associated with CVS are unclear. The number of clips used and the temporary occlusion of the parental artery were reported to be statistically associated with the incidence of vasospasm [7]. This is consistent with the data in Table 1, wherein multiple clips and temporary artery occlusion are used in 7 and 5 patients (except those with unknown data), respectively, among the 9 cases. In addition, female patients and those receiving surgical clipping treatments seemed more susceptible to delayed CVS.

Of the 9 included cases, postoperative SAH and hematoma formation were noted in 2 patients, respectively, rendering the causes of vasospasm complicated and debatable. The epidural hematoma was found in a postoperative head CT in 2 patients including ours, although it seemed unrelated to the development of vasospasm. Any sign of hemorrhage in the subarachnoid or parenchymal space was not seen in the other cases. Therefore, as Hashimoto et al. [3]. Concluded, factors other than operation-related hemorrhage might play a role in vasospasm.

Approximately 40 years ago, a “hypothalamic” theory was proposed that mechanical or vascular compromise of the hypothalamus during aneurysm clipping could promote the release of certain mediators, causing vasospasm [12]. However, this theory could not explain that the distribution of CVS is regional in most cases. This conclusion was in compliance with that of Paolini et al. that factors in the proximity of an aneurysm are most likely the source of the spasm [6].

Neurogenic vasospasm is another potential mechanism. The innervation of extra-parenchymal part of the cerebral arteries contains three types of fibers, sympathetic, parasympathetic, and sensory, which originate either in the superior cervical ganglion, sphenopalatine and otic ganglion, or trigeminal ganglion [13]. The neu-
Symptomatic vasospasm with an unruptured aneurysm

Table 1. Characteristics of the reported cases with delayed symptomatic vasospasm for unruptured aneurysms after uneventful surgeries

<table>
<thead>
<tr>
<th>Author</th>
<th>Age (Year)/Sex</th>
<th>Spasm Syms</th>
<th>Aneurysm location</th>
<th>TCoP</th>
<th>Clip No</th>
<th>Syms Onset (POD)</th>
<th>PO finding</th>
<th>Treatments</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Our case</td>
<td>50/M</td>
<td>Headache, aphasia, L. hemiparesis</td>
<td>R. M2</td>
<td>N</td>
<td>2</td>
<td>10th</td>
<td>EDH</td>
<td>Volume expansion, antiplatelet, hyperbaric oxygen</td>
<td>Mild to moderate weakness</td>
</tr>
<tr>
<td>Yang [5]</td>
<td>61/F</td>
<td>Aphasia, Mental change</td>
<td>L. MCA bif</td>
<td>Y</td>
<td>3</td>
<td>10th</td>
<td></td>
<td>Hydration, antiplatelet, chemical angioplasty</td>
<td>Aphasia (partially)</td>
</tr>
<tr>
<td>Kitazawa [7]</td>
<td>63/F</td>
<td>Aphasia, R. hemiparesis</td>
<td>L. ParCA</td>
<td>Y</td>
<td>2</td>
<td>5th</td>
<td>EDH</td>
<td>Triple H</td>
<td>Fully</td>
</tr>
<tr>
<td>Kitazawa [7]</td>
<td>53/F</td>
<td>Aphasia</td>
<td>L. ParCA</td>
<td>N</td>
<td>3</td>
<td>9th</td>
<td>SAH</td>
<td>Triple H</td>
<td>Fully</td>
</tr>
<tr>
<td>Kitazawa [7]</td>
<td>21/F</td>
<td>Aphasia, Gerstmann syndrome.</td>
<td>L. ParCA</td>
<td>Y</td>
<td>1</td>
<td>12th</td>
<td></td>
<td>Chemical angioplasty, hyperbaric oxygen, Triple H</td>
<td>Fully</td>
</tr>
<tr>
<td>Bloomfield [8]</td>
<td>54/F</td>
<td>L. hemiparesis</td>
<td>R. MCA bif</td>
<td>Unknown</td>
<td>2</td>
<td>9th</td>
<td></td>
<td>Volume expansion, dexamethasone</td>
<td>Mild weakness</td>
</tr>
</tbody>
</table>

Abbreviations: Syms, symptoms; TCoP, temporal clipping of parental artery; PO, postoperative day; PO, postoperative; ICA, internal carotid artery; PCoA, posterior communicating artery; MCA, middle cerebral artery; ParCA, paraclinoid carotid aneurysm; EDH, epidural hematoma; SAH, subarachnoid hemorrhage; Bif, bifurcation; L, left; R, right; Y, yes; N, no; M2, M2 segment of MCA.
Symptomatic vasospasm with an unruptured aneurysm

Regulatory regulation is crucial for the brain to maintain the optimal cerebral blood flow (CBF) under physiological conditions [13-15]. Sympathetic fibers play a role in reducing CBF under the stimulation while parasympathetic and sensory fibers act contrary [15-17]. The dysregulation of this complex network in the pathological situations can cause alterations in CBF, which is involved in the pathogenesis of delayed vasospasm during SAH [18]. During surgical clipping for an aneurysm, procedures such as arachnoid dissection, artery manipulation, or temporal occlusion could affect the nervous control of the vessels. This may also clarify the occurrence of the vasospasms after open surgery, with most of them being regional, and the disturbance of the sensory fibers may account for the headache in some patients. Paolini et al. [6]. Hypothesized that clipping itself could stimulate the nerve endings of the trigemino-cerebrovascular system and cause a marked release of vasodilatory peptides. The heterogeneous latency of the vasospasm was based on the temporal pattern of vasoactive peptide depletion. Nevertheless, we speculate that since the cerebral arteries are innervated by fibers of different functions, surgical manipulation, local aseptic inflammation, and potentially some unknown factors may result in a dysregulation or even denervation of the arterial nervous system, causing vasospasm in some patients. The severity and duration of the spasm depend on the extent of the combined effects of this disturbed network and duration required to return to the baseline.

In our case, the newly onset headache occurred on the 7th postoperative day and was treated with Saridon. However, the patient did not get a complete relief from the pain and developed ischemic neurological symptoms 3 days later. This was in agreement with the hypothesis by Hashimoto et al. that a prolonged and unexpected headache after uncomplicated clipping might be a warning sign of vasospasm [3]. Although a warning headache was not referred to in the other 7 cases, this could be attributed to a postoperative headache as compared to neurological deficits, which was often considered a normal surgery-related reaction similar to our case. In consideration of the possible disastrous consequences of subsequent CVS, newly onset headache, especially when unexplainable by surgery, should be focused upon for early detection and treatment of vasospasm.

Delayed neurological deficits secondary to SAH arises from extremely sophisticated mechanisms other than vasospasm itself [19]. One of the supporting evidence is the study on endothelin receptor antagonists both in animal models and human showing a reduced vasospasm but no improvement in functional outcome post SAH [20, 21]. A systematic review and meta-analysis of the clinical trials indicate nimodipine as the only effective treatment [22, 23]. Little experience has been accumulated with regard to the management of delayed CVS for UIAs. Since brain injury caused by CVS for UIAs is completely different from that in SAH in terms of lacking damaging effects from early brain injury and toxic products from the blood, it is reasonable to speculate the former may mainly occur due to the vasospasm-induced cerebral blood flow reduction. Treatments aiming to dilate vasospastic arteries, which are not beneficial to SAH patients may thus be effective for those with UIAs.

The previously reported cases were treated either with volume expansion, triple H, antiplatelet, intravenous or intra-arterial administered vasodilators. Some were treated with a combination of these methods, and all of them responded with good recovery. However, our case did not recover adequately from conservative treatments, thereby rendering angioplasty as a suitable option; also, whether chemical or mechanical treatment should be considered in the case of progressively worsening symptoms. Nevertheless, the efficiency of these treatments remains to be tested in larger studies and optimized in randomized controlled trials.

Conclusions

CVS associated with unruptured aneurysms is extremely rare; however, the number of incidences may be underestimated and may be expected to increase due to frequently performed DSA and additional attention focused on this entity. We speculate that the pathogenesis was a multifactor contributing process, among which the dysregulation of the nervous network of the cerebral artery resulted from surgery might be crucial or even dominant. Although due to lack of convincing evidence,
Symptomatic vasospasm with an unruptured aneurysm

positive treatments (for example, volume expansion, vasodilators administration, intra-arterial angioplasty) are recommended to ensure favorable outcomes.

Acknowledgements

This work was supported by The Department of Education of Zhejiang Province (grant numbers: No. Y201432472, No. Y201431989) and The Department of Health and Family Planning Commission of Zhejiang Province (grant number: No. 2014KYB122).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yili Chen, Department of Neurosurgery, The Fourth Affiliated Hospital of Zhejiang University School of Medicine, Yiwu 322000, Zhejiang, China. Tel: +86-18867961092; Fax: +86-21-57643271; E-mail: chenyili70@gmail.com

References

Symptomatic vasospasm with an unruptured aneurysm
