To investigate the possible causes of a false-negative initial cerebral digital subtraction angiography (DSA) of aneurysmal subarachnoid hemorrhage (SAH).

Six initially unrecognized ruptured aneurysms were reviewed from among approximately 160 aneurysmal SAH cases collected from the medical records. The standard angiographic procedure and findings on repeat DSA were used to identify the possible causes.

The initial DSA was reviewed and the false-negative impression resulted from an initial overlooking with or without incomplete procedure (4/6), presumed thrombosis or vasospasm with no recognized aneurysm, even when reviewed retrospectively (3/6), and the presence of a blister aneurysm (1/6). Two of the six cases had multiple causes.

Whenever the DSA is negative in a patient strongly suspected of an aneurysmal SAH, the three above-mentioned causes should be considered and repeat DSA in the proper clinical setting is recommended.

Roughly 15~30% of the initial cerebral digital subtraction angiography (DSA) performed in patients with subarachnoid hemorrhage (SAH) fails to show a cause [1-3]. These DSA-negative SAH patients have a better prognosis if no aneurysm is found on repeat DSA [4]. In clinical practice, however, the etiology of SAH in this patient group must be zealously considered to avoid the devastating medical and legal consequences that result from an interpretation error. In 2002, Friedman et al. recommended selective repeat DSA when (1) vasospasm compromised the first study, (2) part of the cerebral circulation is not seen well, (3) CT shows a large diffuse or focal SAH, and (4) a second SAH occurs (5). To verify these recommendations, we retrospectively reviewed six patients with ruptured cerebral aneurysms with an initial false-negative DSA. The analysis focused on the causes of failure to make the correct diagnosis of ruptured aneurysm. We hope to enhance our diagnostic ability when future cases are encountered.

MATERIALS AND METHOD

Patients
The study was approved by the local institution review board. This retrospective study included personally experienced cases with initial negative DSA findings in which the diagnosis of cerebral aneurysm rupture was confirmed at subsequent endovascular or surgical intervention seen from 2005 to 2009. The subjects were five females and one male ranging in age from 39 to 71 years. Inclusion criteria were patients with SAH, with an inconclusive diagnosis on the initial DSA, but who were later proven to have a ruptured cerebral aneurysm based on repeat DSA.

The exclusion criteria included (1) a diagnosis of ruptured cerebral aneurysm made on the initial
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DSA, (2) the initial DSA was not performed at our hospital, and (3) the diagnosis of ruptured cerebral aneurysm was made by magnetic resonance angiography (MRA) or CT angiography (CTA), not by DSA.

CT and cerebral DSA findings

All six cases had similar SAH distribution patterns on CT, consisting of a more than 10-mm-thick, dense blood clot primarily accumulated in the anterior interhemispheric and anterior suprasellar cistern. None had a SAH distribution pattern confined to the perimesencephalic or ambient cistern. For SAH patients with suspected ruptured aneurysms, plain CT (without CTA) was performed, followed by cerebral DSA within 6 hours. In agitated patients, DSA was performed under general anesthesia, preferentially. For better scrutinizing the aneurysm and parent artery in the circumferential direction, the additional three-dimensional (3D) rotational angiography was performed in some cases (case 2 and case 4) in the initial DSA, and all cases in repeat DSA. The initial DSA studies were reviewed by one senior interventional neuroradiologist (HF Wong) with more than 20 years of experience to determine if the DSA studies were performed incompletely or were essentially negative. The incomplete study was defined as suboptimal imaging quality, mal-positioning or the unfulfilled 4-vessel cerebral angiography. Repeat DSA was done a few days to 2 weeks later depending on the clinical and imaging scenario (Table 1), such as a sudden deterioration in the clinical condition or mitigated vasospasm based on the transcranial Doppler sonography findings. Unlike the initial angiography, the repeat DSA used an appropriate technique, and included complete four-vessel DSA, 3D rotational angiography, or other techniques, including cross compression of the contralateral carotid artery and a higher injection rate [4, 6]. To exclude the rare possibility of SAH related to a dural arteriovenous fistula, external carotid angiography was included in the repeat DSA in some cases.

RESULTS

In our series, approximately 3.75% of the proven cases of aneurysmal SAH had an initial false-negative DSA. The possible causes of unrecognized ruptured aneurysms included (1) an initial overlooking, (2) thrombosis or vasospasm as the aneurysms were still not identified on retrospective scrutiny, and (3) the presence of a blister aneurysm. Some cases may have multiple causes. 3D rotational angiography was performed only in cases 2 and 4. Of the six cases, three false-negatives were attributed to early vasospasm or thrombus that obscured the aneurysm sacs. In case 2, there was a small mass effect encircled by the bowed anterior cerebral artery with tangible stasis of contrast medium in the late arterial phase and no connection to adjacent major parent arteries (Fig. 1a-f). Cases 4 and 5 had similar findings with a small amount of amorphous contrast pooling antero-inferiorly to the anterior communicating artery on the initial DSA that turned out to be the culprit aneurysm on repeat DSA (Fig. 2a-d). Case 1 presented with aneurysms just behind the genu of the internal carotid artery that arose from the fenestrated anterior communicating artery; these could not be diagnosed confidently without 3D rotational angiography. Case 3 was later recognized as blister aneurysms that eluded attention on the initial DSA. The ruptured aneurysms were much larger on the repeat DSA.

DISCUSSION

The most majority of the articles pertaining to the value of repeat angiography in the cases of unexplained SAH were back to 20 years ago with the ruptured aneurysms found by repeat DSA within 5% from western authors and up to 22% from Japan [1, 7-10]. No matter the pro and con opinions for the repeat DSA were concluded, it was generally accepted that the repeat DSA can be justified only when the initial DSA was technically inadequate and when vasospasm was present. In recent years, this topic has renovated by the introduction of some state-of-art techniques including 3D rotational angiography and CTA [6, 11-13]. Although not as persuasive as did with previous large-scale studies, we tried to categorize the causes and designed a flowchart for the decision-making in a more explicit way (Fig.3).

For patients with a spontaneous SAH with an initial inconclusive result, many institutions perform a repeat DSA in 7–10 days, unless the bleeding source is identified by another modality or re-bleeding is evident on CT during the observation interval [14]. The goal of repeat DSA is to detect or exclude the presence of an aneurysm with more confidence, albeit at the potential risk of intrinsic DSA-related complications. Although there is a role for CTA in detecting ruptured aneurysms using state-of-the-art CT hardware and
Table 1. ICA: internal carotid artery; MCA: middle cerebral artery; Acom: anterior communicating artery.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Aneurysm site</th>
<th>CT SAH pattern</th>
<th>Note</th>
<th>Aneurysm overlooked on initial DSA</th>
<th>No aneurysm seen on initial DSA, presumably related to vasospasm or thrombus</th>
<th>Blister aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>50</td>
<td>Lt siphon ICA</td>
<td>Anterior suprasellar cistern, a little more on the left side</td>
<td>A small aneurysm, unrecognized on initial DSA, just behind the ICA genu. 3D rotational angiography not performed. Altered mental status prompted 2nd CT and DSA in which the rebleeding and growing aneurysm were noted respectively.</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>45</td>
<td>Lt supraclinoid ICA</td>
<td>Symmetric, thick SAH in anterior and posterior suprasellar cistern</td>
<td>Initial DSA showed no discrete aneurysm, but mass effect around supraclinoid ICA and ACA, A1 segment</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>41</td>
<td>Lt MCA</td>
<td>Anterior suprasellar cistern and left Sylvian fissure cistern</td>
<td>A blister aneurysm eluded attention on initial DSA. The ruptured aneurysm become larger on repeat DSA.</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>39</td>
<td>Acom</td>
<td>Thin SAH in ventral interhemispheric fissure and anterior suprasellar cistern</td>
<td>Initial DSA showed no aneurysm even with 3D rotatory angiography scrutiny. Repeat DSA disclosed a discrete saccular Acom aneurysm associated severe vasospasm of the parent ACA, bil</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>62</td>
<td>Acom</td>
<td>Thin SAH in ventral interhemispheric fissure</td>
<td>Initial DSA showed no discrete aneurysm, possibly due to vasospasm-caused insufficient contrast opacity of aneurysm and parent artery. 3D rotational angiography survey not performed. Acom aneurysm with severely narrowed ACAs showed on repeat DSA.</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>42</td>
<td>Acom</td>
<td>Symmetric, thick SAH in anterior suprasellar and ventral interhemispheric cistern</td>
<td>Suboptimal imaging quality and unfulfilled 4-vessel DSA procedure due to patient’s agitated state and unstable vital sign. 3D rotational angiography survey not performed.</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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post-processing [15], many neurosurgeons and radiologists still prefer DSA for both diagnostic and treatment purposes. In some clinical settings, CTA is redundant because DSA still needs to be performed following either negative or positive findings on CTA. In addition, CTA is less reliable in the presence of vasospasm, small aneurysms, and the inability to evaluate collateral flow through the circle of Willis. Currently, using DSA is considered the gold standard for searching for possible cerebral aneurysms in acute-onset SAH because all of the intracranial vessels, including the communicating arteries and tertiary cortical arterioles, can be examined thoroughly. Moreover, DSA is regarded as a one-stop procedure, i.e., it is both a diagnostic tool and allows instant endovascular intervention if the culprit ruptured aneurysm is suitable for this less invasive treatment.

With the continuing technical refinement of cerebral DSA in terms of imaging acquisition,
Figure 2. In case 5, a. Initial CT image revealed thick SAH evenly present in bilateral basal cistern and ventral inter-hemispheric fissure cistern. b. Initial DSA misinterpreted left ICA blister aneurysm (arrow) responsible for causing SAH while the faint small perforator-like structure (arrowhead) in the expected Acom was overlooked. c. Repeat DSA showed a small Acom aneurysm (arrowhead) on 3D rotational angiography, along with vasospasm-caused luminal narrowing of bilateral anterior cerebral arteries (15 days later). d. Coil embolization of the culprit Acom aneurysm (arrow).

Figure 3. DSA to aneurysm diagnosis
resolution, and post-processing, the rate of initially false-negative angiograms in aneurysm detection has declined significantly from 10–23% to less than 2%, where an aneurysm is found on repeat DSA [2-3]. In our cases, false-negative DSA was uncommon, and only six cases were seen over a 5-year period in a neuroradiological practice at a major medical center. The aim of our retrospective evaluation of these cases is to remind the readers of the possible causes of a false-negative interpretation. If a similar condition is encountered, a repeat DSA or more detailed workup is necessary.

We identified three main causes of a false-negative result on the initial DSA: (1) an overlooking with or without incomplete procedure, (2) an obscured aneurysm, even when scrutinized retrospectively, and (3) the presence of a blister aneurysm. These three causes can be related to each other.

A comprehensive training program and good quality control for any imaging modality are always necessary for maintaining high radiological diagnostic accuracy. As at other institutions, the DSA suite provides a full-time service for angiographic diagnosis and treatment. This can be accomplished only by teamwork involving a large staff, including both senior and junior employees. As is the case with the misinterpretations happening in other imaging studies, one of the most important causes of the initial false-negative study is the unintentional overlooking, that is “the reader is not looking hard enough” described by some authors [16]. Whenever the preliminary negative DSA result was made, a strict audit mechanism should be operated before a timely final or revised impression being notified to the clinicians. To overlook the abnormal finding will become more often in case of an incomplete procedure such as the suboptimal imaging quality, mal-positioning or the unfulfilled 4-vessel cerebral angiography. Since the patients with a false-negative DSA due to incomplete procedure for the under-recognized ruptured aneurysm are at very high risk of re-bleeding before the scheduled repeat DSA, we recommend that these patients have the second DSA done right away. The recent technical advances in 3D rotational angiography make it a necessary part of comprehensive cerebral DSA, especially for detecting small aneurysms at atypical sites [12]. The more comprehensive the DSA study performed, the lower the chance of misinterpretation.

The obscure aneurysm that is not recognized on initial DSA presumably results from vasospasm of the parent artery or transient thrombosis of the ruptured aneurysm. Insidious vasospasm or thrombosis episodes may lead to narrowing of the aneurysm neck, thrombosis of the aneurysm sac or parent artery, or even destruction of the aneurysm after it bursts with spontaneous thrombosis of aneurysm [8]. Previous studies have postulated that extraordinary disparity in the dome-to-neck ratio of the ruptured aneurysm and the contrast medium viscosity influenced the findings [17-19]. In this setting, the thrombosed aneurysm will not be manifested even on 3D DSA. While vasospasm is generally thought to peak 1 to 2 weeks after aneurysm rupture, it is generally accepted that vasospasm will hamper the aneurysm treatment because the collateral flow will be inadequate and an endovascular approach is unavailable. Early-onset vasospasm that turns out to be the prime cause of a false-negative initial DSA is easily overlooked and barely mentioned before in one book section in 2002 [5]. We suggest routinely looking for the angiographic signs of vasospasm, even if subtle, such as non-visualization or displacement of the parent arteries or abnormally retained contrast medium anywhere in the suprasellar cistern. Since a large SAH burden is considered to be a reliable predictor of vasospasm, any interpreter, when observing a large pooled SAH on the initial CT scan, cannot rashly rule out a “hidden ruptured aneurysm” or conclude that the initial DSA is negative [20]. Once vasospasm or thrombosis is considered the cause of an inconclusive DSA result, the repeat DSA should be done as soon as prudent. Based on the lesson taught by our cases, the risk of re-bleeding is high, within 1 or 2 weeks, when the vasospasm or thrombosis resolves before expected.

Blister aneurysms, i.e., aneurysms with a thin wall and no neck, commonly arise from non-branching sites along the circle of Willis. They differ from the frequently encountered saccular aneurysms morphologically, histologically, and even in terms of treatment strategy [21-22]. The inherent small size and atypical location are easily missed on conventional DSA, and rotational angiography followed by advanced 3D post-processing is considered useful for aneurysm detection. Experienced neuroradiologists should review any apparently negative DSA study before giving the final impression.

Contrary to the treatment strategy following a positive DSA result, the options after a negative DSA for the subsequent diagnosis and treatment strategy may vary, depending on the patient and institution. As imaging interpreters, radiologists and
neurosurgeons should check the above-mentioned potential pitfalls before making a decision. While waiting for the next intervention procedure, like repeat DSA, the clinician should focus on other etiologies of a spontaneous SAH. Sometimes, enhanced CT or magnetic resonance imaging (MRI) studies and laboratory data can aid in differentiating vascular malformations, neoplasms, meningoencephalitis, coagulopathy, and even pituitary apoplexy.

**CONCLUSION**

With the advances in DSA equipment and post-processing workstations, false-negative DSA for detecting a ruptured aneurysm is rarely encountered. The causes include blister aneurysms, early-onset vasospasm/thrombosis, and an initial overlooking with or without the incomplete procedure. We suggest that these causes be kept in mind with an initial negative DSA with a SAH distribution typical of a ruptured aneurysm. These patients must be approached proactively, in the hope of precluding re-bleeding and improving the patient outcome.

**REFERENCES**

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腦血管攝影檢查未能發現的動脈瘤破裂所引起的蛛網膜下腔出血：回溯性研究

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長庚大學 林口長庚醫院 影像診療部\textsuperscript{1}
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調查初次腦血管攝影未能診斷動脈瘤的原因。
在 160 位診斷為動脈瘤破裂所致蛛網膜下腔出血病例中，找到 6 位在首次腦血管攝影檢查未能找到原因的病患。我們以標準的腦血管攝影步驟與第二次血管攝影檢查的發現，試圖找出在首次腦血管攝影檢查未能找到動脈瘤的原因。

首次腦血管攝影檢查未能找到出血動脈瘤的原因有：誤判與不完全的操作程序 (4/6)，疑似動脈瘤血栓或血管痙攣而遮蔽了動脈瘤 (3/6)，水泡狀的動脈瘤 (1/6)。在兩個病例中存在有多重的原因。

如果在臨床上懷疑是因動脈瘤破裂所造成的蛛網膜下腔出血，我們建議在首次腦血管攝影沒有異常發現的病例，必須要考慮是否有以上所述的 3 個可能原因，以做為是否要重複施行腦血管攝影的參考。