

Use of Follow-Up Imaging in Isolated Perimesencephalic Subarachnoid Hemorrhage

A Meta-Analysis

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Background and Purpose—Multiple studies have shown that negative computed tomographic angiograms (CTAs) are reliable in excluding aneurysms in patients with isolated perimesencephalic subarachnoid hemorrhage (pSAH). We evaluate the use of digital subtraction angiography versus CTA for initial diagnosis and of angiographic follow-ups in patients with pSAH by performing an institutional analysis and a meta-analysis of literature.

Methods—Retrospective institutional analysis of patients with pSAH was performed from 2008 to 2014. The number and types of follow-up imaging studies were tabulated. Initial and follow-up studies were evaluated by an experienced neuroradiologist for intracranial aneurysm. Meta-analysis of literature was performed to assess the use of initial digital subtraction angiography and of follow-up imaging.

Results—Our institutional review revealed no additional use of initial digital subtraction angiography or of any angiographic follow-up after initial negative CTA in patients with pSAH on noncontrast CT. Meta-analysis of 40 studies yielded a total of 1031 patients. Only 8 aneurysms were first diagnosed on follow-ups (0.78%). Careful review showed that some of these aneurysms reported on follow-up are of questionable validity. Initial digital subtraction angiography and follow-up imaging after a negative initial CTA showed no statistically significant benefits.

Conclusions—In patients meeting the strict imaging criteria of pSAH, initial negative CTA is reliable in excluding aneurysms. A critical review of the literature through meta-analysis shows no foundation for multiple follow-up studies in patients with pSAH. (*Stroke*. 2015;46:401-406. DOI: 10.1161/STROKEAHA.114.007370.)

Key Words: angiography, digital subtraction ■ meta-analysis

The isolated perimesencephalic subarachnoid hemorrhage (pSAH) pattern was first described as a distinct imaging and clinical entity by van Gijn et al¹ in 1985. It is defined as the presence of blood confined primarily in the perimesencephalic cistern, anterior to the brain stem, with possible extension to ambient cisterns or proximal stems of the sylvian fissures but without extension to lateral parts of the sylvian fissures, anterior interhemispheric fissures, or lateral ventricles. The pSAH pattern is seen in 5% of patients with SAH, with an annual incidence of ≈0.5 per 100 000 patients.²

Over the past decade, advances in computed tomographic angiographic (CTA) technology, with better contrast bolus timing and 64-row detector arrays, have allowed for aneurysms to be diagnosed with ≈100% sensitivity in ≈10% of patients with pSAH caused by aneurysmal bleeding.³⁻⁷ Multiple studies have shown the reliability of CTA in excluding aneurysms in patients with SAH and the futility of multiple follow-up examinations in patients with pSAH.⁸⁻¹⁰ In 2009, Agid et al⁸ concluded that digital subtraction angiography (DSA) and subsequent imaging are not required in patients with pSAH

after negative CTA. Notwithstanding, practice patterns have been slow to change on the need for initial DSA and extensive angiographic follow-up in these patients.

We performed a retrospective review of patients with pSAH in the past 6 years at our institution. We then performed a meta-analysis of the literature, critically reviewing the follow-up studies in patients with pSAH, to assess the use of follow-up imaging for aneurysm detection in patients with pSAH.

Methods

Institutional Study

A retrospective keyword search was performed for reports containing the words perimesencephalic, prepontine, or pretruncal in the past 6 years at our single, large, multisite, academic institution after obtaining Institutional Review Board approval with waiver of consent. Inclusion criteria consisted of patients with perimesencephalic pattern of blood on initial noncontrast CT undergoing CTA and DSA within 24 hours of admission and additional follow-up angiographic imaging. Patients with history of trauma, diffuse SAH, thick blood above the perimesencephalic cistern, and intraventricular blood were excluded. Two-hundred fourteen CTA reports met keyword search

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criteria. Images from these reports were reviewed to determine whether the hemorrhage pattern met the above-described definition of pSAH. A total of 18 patients met inclusion criteria. The number and types of follow-up imaging studies, including CT/CTAs, MRI/magnetic resonance angiograms (MRAs), DSAs, and transcranial Dopplers, performed on these patients were tabulated. All initial and follow-up studies were evaluated for intracranial aneurysm by an experienced neuroradiologist. Follow-up studies were assessed for any positive diagnostic yield.

All CTA examinations were performed on 64-section multidetector CT scanners (General Electric Lightspeed, Milwaukee, WI) using similar protocols. Scanning was performed from the base of C2 to the calvarial vertex. Intravenous contrast, iohexol (Omnipaque 300/350; Nycomed Amersham, Oslo, Norway), was administered by using a dual-power injector with an injection rate of 4 mL/s for a total volume of 60 mL for Omnipaque 350 and 75 mL for Omnipaque 300 and then followed by a saline chaser of 80 mL. The SmartPrep technique (GE Healthcare, Milwaukee, WI) was used to adequately time the bolus of contrast. The protocol for data acquisition was helical mode, 0.5-s gantry rotation time, 32×0.625-mm collimation, 0.5 to 1 pitch, 0.625-mm section thickness, and 0.315-mm reconstruction interval. Acquisition parameters were 100 to 120 kV and 300 to 660 mA, a head filter with a display field of view of 15 cm, and a standard reconstruction algorithm. Images were reformatted in axial, sagittal, and coronal 2.5-mm-thick maximum intensity projections with 50% overlap, as well as 3-dimensional (3D) surface-rendered and volume-rendered reconstructions, using Advantage Workstation (GE Healthcare) and Vitrea 2 workstation (Vital Images, Plymouth, MA).

DSA was performed by using a single dedicated biplane neuroangiographic unit (Siemens Axiom Artis zee; Siemens, Erlangen, Germany) with an image intensifier matrix of 1024×1024 pixels. Cerebral angiography included rotational spin angiography with 3D reconstructions (DynaCT; Siemens, Erlangen, Germany). Intravenous contrast, iohexol (Omnipaque 240; Nycomed Amersham, Oslo, Norway), was injected with a dual-power injector.

Meta-Analysis

Meta-analysis was performed based on literature search for patients with pSAH with imaging follow-up. A keyword search was performed with terms subarachnoid hemorrhage (MeSH) (perimesencephal* or pretrunc* or [angiogra* and negative] or [angiogra* and occult] or mesencephalon [MeSH]) and cerebral angiography (MeSH) in Medline (241 entries), Embase (593 entries), Cochrane Library (116 entries), Scopus (147 entries), and Web of Science (403 entries). These 1500 search results from the 5 major databases and related articles for additional references not in our initial search results were reviewed for relevance. Studies with no follow-up studies performed, <5 patients with pSAH, unspecified percentage of patients lost to follow-up, and those with cerebrospinal fluid xanthochromia without pSAH on CT were excluded. In cases of disagreement between the authors on which studies should be included in the analysis, consensus was reached by discussion. A flowchart of the search is presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement, as shown in Figure 1.

Our final analysis included 40 studies, including our institutional data, with 2 articles in German.^{6–8,11–46} Articles were evaluated on the number of patients with pSAH, the modality of initial and follow-up imaging, and their yield. Patients were grouped into those with DSA only, with CTA only, and those with both DSA and CTA as initial studies. These 3 groups were then subgrouped if their follow-up studies were DSA only, CTA only, or DSA and CTA combined. The MRI/MRA follow-up was not included because of its lower sensitivity.⁴⁷ Age and sex data were recorded when available, and the overall sex ratio and mean age were calculated based on only studies with demographic information specific to the pSAH group. Neurological deficits and outcomes were not evaluated. All statistical analyses were performed using Excel (Microsoft, Redmond, WA) and SPSS software version 19.0 (IBM, Armonk, NY). Two-way ANOVA of

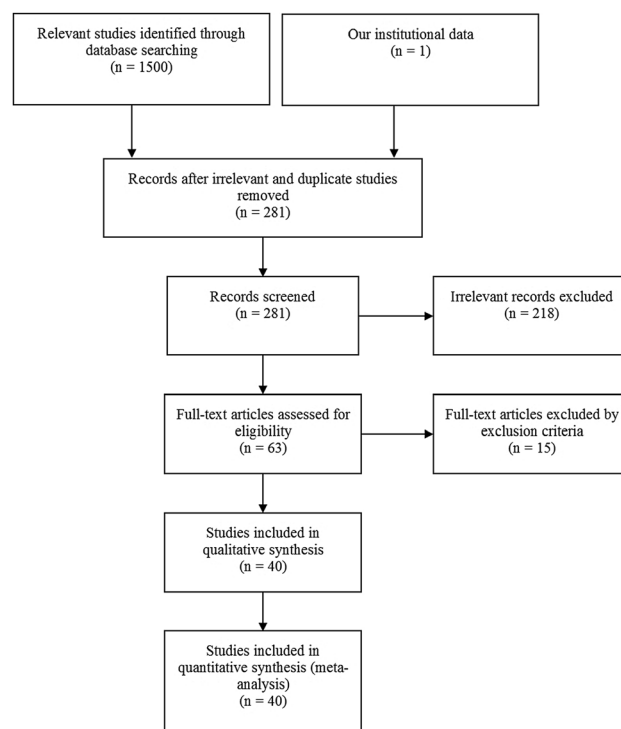


Figure 1. Flow chart of meta-analysis search.

the aneurysm detection rate based on initial and follow-up protocols was used to evaluate the effects of each initial and follow-up imaging strategy. Continuous variables (aneurysm detection rate, age, and sex ratios) were expressed as the mean±SD or the median with a range, and categorical variables (number of studies and work-ups) were expressed as counts and percentages. The 95% confidence intervals for each subgroup were calculated using the normal approximation interval. The heterogeneity of studies included in meta-analysis was analyzed by using the *I*² analysis based on continuous χ^2 statistics. The risks of bias within individual studies and across studies were also assessed.

Results

Institutional Study

Eighteen patients met inclusion criteria for isolated pSAH (Figure 2). Ten men and 8 women had a mean age of 49.3±13.1 years. All patients had initial negative CTAs and DSAs and subsequently underwent extensive follow-ups, including DSA, CTA, MRA, transcranial Doppler, and miscellaneous studies, such as MRA of neck.

There were a total of 38 follow-up CT/CTAs, 20 MRI/MRAs, and 16 DSAs, resulting in an average of 2.11 CT/CTAs, 1.11 MRI/MRAs, and 0.89 DSAs per patient. No aneurysms (or other culprit vascular lesions) were detected on any of the follow-up imaging. Sixteen transcranial Dopplers performed in 8 patients showed mild middle cerebral artery vasospasms in 4 patients, which all spontaneously resolved without intervention. No patients had clinically significant hydrocephalus.

Meta-Analysis

A total of 1440 patients were included in the 40 studies (including our institutional review) with a male:female ratio

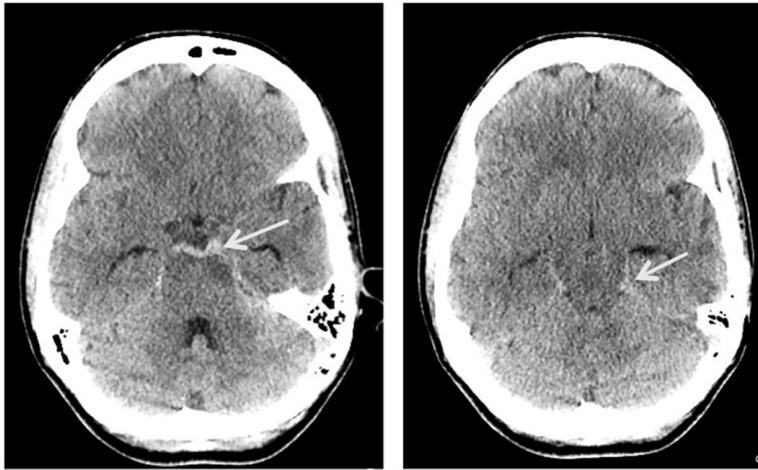


Figure 2. Computed tomographic (CT) scan of a patient from institutional study: a 46-year-old woman presenting with thunderclap headache. Noncontrast CT showed hyperdense blood centering in the preponine cistern and extending to the bilateral ambient and quadrigeminal cistern with mild ventricular dilation.

of 55.6:44.4 and a mean age of 51.9 years. Thousand and thirty-one of these 1440 patients had follow-up imaging, with DSA, CTA, or both DSA and CTA. Of these 1031 patients, a total of 8 aneurysms in 8 patients were reported to be first discovered on follow-up imaging in 6 studies. This corresponds to a reported rate of aneurysm first detected on follow-up imaging of 0.78% (95% confidence interval, 0.23%–1.32%), with subgroup analysis as described in the Table and Figure 3.

The 2-way ANOVA test yielded a *P* value of 0.353 for the 3 initial diagnostic strategies, 0.701 for the 3 follow-up strategies, and 0.916 for the interaction term of initial and follow-up strategies. There was no statistically significant benefit of performing DSA during the initial evaluation or of any follow-up angiographic studies. The *I*² test recommended by Cochrane Reviews to assess inconsistency in meta-analysis yielded 16.6%, reflecting low heterogeneity among the meta-analysis studies.⁴⁸ All studies included in the meta-analysis were retrospective reviews of institutional experiences, leading to low risks of bias both within and across individual studies.

Discussion

Patients with pSAH typically present with minimal clinical symptoms (Hunt and Hess scale 1), no focal neurological deficits, and no loss of consciousness.⁴⁹ The isolated perimesencephalic pattern has a better prognosis than other subtypes of SAH, with hydrocephalus and symptomatic vasospasm being decidedly uncommon on follow-up.^{45,50}

Although the cause of pSAH remains elusive, multiple studies have suggested a venous origin for a majority of

pSAH cases. Because 10% of posterior circulation aneurysms present with a perimesencephalic bleeding pattern, some angiographic imaging is essential, but the use of additional angiographic studies is debated.^{5–7,51–54}

Controversy centers around how frequently aneurysms are not present on the initial CTA and are only detected on follow-up angiographic examinations, despite multiple studies showing that CTA is sensitive in detecting small aneurysms (including those in posterior circulation sometimes responsible for pSAH).^{30,53,55,56}

Rinkel et al^{57,58} suggested that patients with pSAH did not need follow-up DSA after initial negative findings on DSA in 1991. Two years later, they suggested that DSA was not needed at either initial or follow-up imaging in patients with pSAH with negative CTA findings.⁵⁹ This recommendation was further corroborated by Ruigrok et al⁶⁰ in 2000, who determined that CTA without additional follow-up was the best diagnostic strategy compared with no angiographic work-up, DSA without follow-up, and CTA with DSA follow-up to exclude aneurysms in patients with pSAH using a mathematical model.

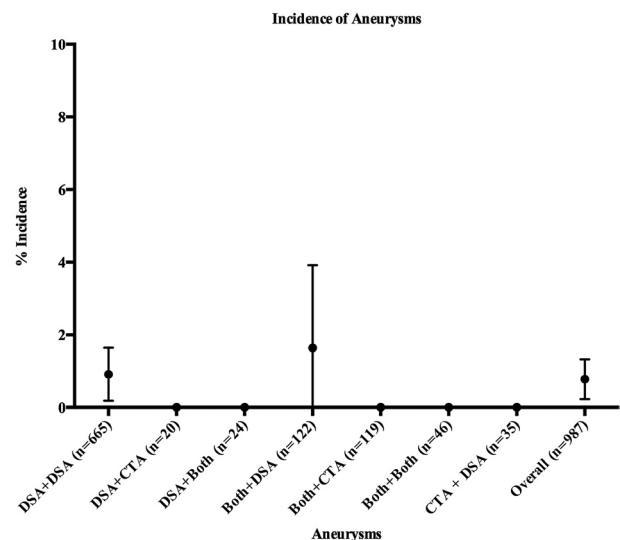


Figure 3. Reported aneurysm detection rate of meta-analysis grouped by initial+follow-up studies. CTA indicates computed tomographic angiography; and DSA, digital subtraction angiography.

Table. Aneurysm Detection Rate by Subgroups Based on the Meta-Analysis Result

	Initial DSA	Initial CTA	Initial DSA and CTA
Follow-up DSA	0.90% (95% CI, 0.18%–1.62%)	0	1.64% (95% CI, 0%–3.89%)
Follow-up CTA	0	No cases reported	0
Follow-up DSA and CTA	0	No cases reported	0

CI indicates confidence interval; CTA, computed tomographic angiography; and DSA, digital subtraction angiography.

In 2006, Kershenovich et al⁶¹ performed a retrospective review of 30 patients with pSAH with negative initial CTA that had multiple subsequent DSAs and found no aneurysms on either initial or follow-up DSA studies, concluding that no follow-up studies were necessary. Westerlaan et al³⁰ in 2007 arrived at the same conclusion after reviewing 30 patients with pSAH and showing no false-negative CTAs. Agid et al⁸ corroborated these findings in 2009, where all 93 patients with pSAH with negative initial CTA had no aneurysms detected on follow-up. Retrospective reviews by Delgado et al¹¹ in 2013 (11 patients), Moscovici et al¹⁶ in 2013 (25 patients), Zhong et al⁴⁵ in 2014 (49 patients), and Yap et al^{62–65} in 2014 (41 patients) and of our institutional data of 18 patients have been performed, and none showed positive findings at DSA or any follow-up imaging studies.

Review of our institutional data with negative CTAs showed no additional benefits of initial DSA or of any follow-up angiographic imaging because no aneurysms were detected in any of these studies. Our meta-analysis of 40 studies, with a total of 1031 patients, also does not demonstrate any additional benefit of performing DSA after a negative CTA at the time of diagnosis and of any angiographic follow-up studies.

The 40 studies in the meta-analysis demonstrated a pooled follow-up detection rate of 0.78% (95% confidence interval, 0.23%–1.32%), which is significantly lower than the often-quoted 1.5% to 3.4% aneurysm detection rate in patients with pSAH on follow-up studies, both based on a single positive case of 29 by Delgado et al²² and 65 by Jung et al.²⁷

Six of the 40 studies described 8 aneurysms and 2 additional vascular abnormalities reported first on follow-up imaging.^{12,21,22,27,36,38}

Andaluz et al¹² ascribed 3 pSAH cases to aneurysms in the anterior circulation, 1 to fibromuscular dysplasia, and the last to a dysplastic basilar terminus. They acknowledged that the fibromuscular dysplasia and dysplastic basilar terminus cases were unconfirmed sources of pSAH. They also conceded that the retrospective review showed aneurysms to be present in the initial study in some cases.¹² Maslehaty et al²¹ ascribed 1 pSAH case to an aneurysm of superior cerebellar artery; however, they did not discuss whether this aneurysm was seen on the initial study. Jung et al²⁷ ascribed 1 pSAH case to an aneurysm of anterior communicating artery, and they were not specific about whether this aneurysm could be seen in the initial study. Anterior circulation aneurysms described by Andaluz et al¹² and Jung et al²⁷ are unlikely to be the causes of pSAH and are likely to be incidental findings. Delgado et al²² and Ringelstein et al³⁸ both ascribed single pSAH cases to an aneurysm of the superior cerebellar artery. Ringelstein et al³⁸ acknowledged that the superior cerebellar artery demonstrated an irregularity on the initial study, whereas Delgado et al²² stated that the aneurysm was not present initially. Both these studies had DSA as the initial evaluation, and given the images provided in these 2 articles, the bolus and the technique (magnification and obliquity) seem different between the initial and follow-up studies. The lack of adequate retrospective review and description renders these initially occult follow-up positive findings of questionable validity. Little et al³⁶ ascribed 1 pSAH case to an aneurysm of the superior cerebellar artery, which was not seen on the initial DSA imaging. A summary table of these 6 articles is presented in Table I in the online-only Data Supplement. The

actual positive rate on follow-up imaging is therefore likely to be even lower than the above-reported rate of 0.78%.

The use of follow-up is dependent on the negative predictive value (false-negatives) of the initial angiographic study. Previous articles have ascribed various sensitivities to CTA using DSA as the reference gold standard, ranging from 92.3% to 96%, with a 61% sensitivity for ≤ 3 -mm aneurysms. These studies did not discriminate between 16- and 64-row fourth- and fifth-generation CTA scanners and older equipment.^{66,67} Modern 16- and 64-row scanners offer a submillimeter resolution of 0.5 to 0.7 mm per detector row.⁴ Previous articles have used the poorer negative predictive values of CTA as a justification for performing additional DSA imaging at the time of diagnosis and multiple follow-up angiographic studies. Newer 64-row CTA scanners have been shown to have an overall per patient aneurysm detection sensitivity and specificity of 99.2%, with 94% sensitivity for aneurysms < 4 mm.⁴ We chose to use these sensitivity and specificity values because currently 16- and 64-slice scanners are the most commonly used equipment.⁶⁸ In addition, all CTA sensitivity and specificity values are based on unspecified DSA technique and equipment, which is an imperfect gold standard. DSA is operator technique- and interpretation-dependent in contrast to CTA that is primarily interpretation-dependent. Monoplane DSA has been described as having a false-negative rate of 7.1% when compared with second examination.³⁷ Even biplane DSA has been shown to miss a significant number of < 3 -mm aneurysms that can be seen on 3D rotational angiography.⁶⁹

Inter- and intraobserver disagreement on whether an SAH pattern is perimesencephalic or diffuse has been cited as a reason to pursue follow-up imaging. Brinjikji et al⁷⁰ found that in the 7 of 8 cases in which there was disagreement on the hemorrhage pattern, the pattern represented diffuse SAH instead of an isolated pSAH pattern. We agree with Agid et al⁸ that whenever a case is ambiguous, it should be regarded as a diffuse aneurysmal pattern. Adoption of this methodology and strict adherence to defining criteria for pSAH should result in minimal intra- and interobserver disagreement. Velthuis et al,⁷¹ who were the first to propose withholding DSA when the patient had a negative CTA, specifically emphasized the importance of maintaining a strict definition of pSAH.

Many studies included in our meta-analysis did not specify the technical parameters used by CTA or DSA. However, this may serve to strengthen our conclusion because angiographic studies performed on older equipment have poorer negative predictive values.

Patients with pSAH have a normal life expectancy and are not at risk of rebleeding.⁷² A meta-analysis of 50 studies, pooling > 4000 patients, shows that rather than repeating the actual study, reinterpretation by a second reader achieves similar results and avoids procedure complications.⁷³ A cost-effectiveness analysis of angiographic imaging in patients with pSAH also shows limited use of multiple follow-up imaging studies.⁷⁴

Repeat imaging can be considered in patients in whom the clinical picture is not consistent with pSAH. Vasospasm and hydrocephalus are infrequent with pSAH.^{45,50} Given the excellent sensitivity and the noninvasive nature of CTA, repeat imaging may be performed preferentially using CTA.⁷⁴

Conclusions

Our institutional study shows no use of initial DSA and of any follow-up angiographic imaging in patients with pSAH with a negative CTA. Our meta-analysis, comprising 40 studies, including our institutional data, and totaling 1031 patients, demonstrates 6 studies with 8 aneurysms seen on follow-up imaging. As discussed above, some of these are of questionable validity.

Given the excellent negative predictive value of modern 16- and 64-row CT scanners, we agree that an initial negative CTA suffices for patients with a strictly defined pSAH pattern when the clinical picture is consistent.⁸ Partial thrombosis and recanalization and growth in a dissecting pseudoaneurysm are potential reasons for missing aneurysms on initial imaging, and follow-up imaging may be considered on a case-by-case basis.

Disclosures

None.

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