Original Article

Detection of unruptured intracranial aneurysms on noninvasive imaging. Is there still a role for digital subtraction angiography?

Oriela Rustemi, Ali Alaraj, Sophia F. Shakur, Jennifer L. Orning, Xinjian Du, Victor A. Aletich, Sepideh Amin-Hanjani, Fady T. Charbel

Department of Neurosurgery, University of Illinois at Chicago, Chicago, Illinois 60612, USA

E-mail: *Oriela Rustemi - orielarustemi@libero.it; Ali Alaraj - alaraj@uic.edu; Sophia F. Shakur - sophia.shakur@uchospitals.edu;
Jennifer L. Orning - jorning@uic.edu; Xinjian Du - xinjian@uic.edu; Victor A. Aletich - valetich@uic.edu; Sepideh Amin-Hanjani - hanjani@uic.edu;
Fady T. Charbel - fcharbel@uic.edu
*Corresponding author

Abstract

Background: To determine the utility of digital subtraction angiography (DSA) in patients with unruptured intracranial aneurysms (UIA) detected on noninvasive imaging, such as magnetic resonance angiography (MRA) and computed tomography angiography (CTA). The follow-up of patients with untreated UIAs involves serial imaging; however, this diagnosis may be based on false positive (FP) results. We examined the incidence of FPs in our institutional series.

Methods: DSAs performed at our institution from January 2011 to June 2014 were retrospectively reviewed and patients referred with UIA detected on noninvasive imaging were selected. Clinical presentation as well as aneurysm location, size, and number reported on DSA and noninvasive imaging were assessed.

Results: Two hundred and eighty six patients (mean age 56.8 years, female 74.8%) with a total of 355 UIA were included. Thirty-one patients had a symptomatic presentation. Analysis per patient showed the pooled FP rate of noninvasive imaging was 15%. MRA FP was 13% (22/171) and CTA FP was 18% (22/120). FP increased significantly with aneurysm size < 3.5 mm on MRA ($P < 0.001$) and <4.0 mm on CTA ($P = 0.01$). Mean aneurysm size among symptomatic patients was significantly larger ($P < 0.001$) as compared to the incidental group (17.8 vs. 7.7 mm). No location was significantly susceptible to false detection of aneurysms.

Conclusion: DSA detection of FP UIA diagnosed on noninvasive imaging is significantly higher for aneurysms <4.0 mm. Accurate diagnosis with DSA may eliminate the need for further follow-up and its associated negative psychological and economic effects. Within the limitations of this retrospective study, we conclude that DSA has a diagnostic role in small aneurysms detected on noninvasive imaging.

Key Words: Angiography, cerebral aneurysm, computed tomography, digital subtraction angiography, magnetic resonance imaging

INTRODUCTION

Noninvasive imaging modalities, such as magnetic resonance angiography (MRA) and computed tomography angiography (CTA), are highly sensitive in detecting unruptured intracranial aneurysms (UIA).[5] In a recent meta-analysis, MRA had 95% sensitivity but specificity varied between 80% and 95%. Eighty-two percentage of

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false positive (FP) aneurysms were <3 mm in size.[12] Although CTA specificity is reportedly higher and less variable,[3,10] this specificity may not apply to small aneurysms.[11] While digital subtraction angiography (DSA) is considered as the gold standard for detecting and imaging UIA, DSA remains an invasive procedure. The differences in the detection of UIA by DSA as compared to MRA and CTA have been previously documented by studies that focused primarily on the overall accuracy and reliability of detection, rather than on FP findings in current practice.[11,13,14] Since the follow-up of patients with untreated UIA involves serial imaging, eliminating FPs diagnosed noninvasively is essential. In this retrospective study, we aimed to determine if there is still a diagnostic role for DSA in patients referred with UIA detected by noninvasive imaging in the current era.

MATERIALS AND METHODS

Patient selection
Following institutional review board approval, all DSA performed at our institution from January 2011 to June 2014 were retrospectively reviewed. During this period, a total of 1395 patients had at least one DSA for various indications. Patients with at least one UIA on noninvasive CTA/MRA (predominantly performed at other institutions) were included. In patients who had both CTA and MRA performed, only the study showing a positive finding was included in the analysis.

Data collection
The location, size, and number of UIA detected by DSA and CTA/MRA were obtained from the imaging reports if available. Clinical data, including presentation and family history of cerebral aneurysm or subarachnoid hemorrhage, was determined from patient charts.

The data were initially analyzed per patient, meaning the aneurysm for which the patient was referred based on noninvasive imaging. The data were then analyzed per aneurysm. In this analysis per aneurysm, secondary false negative (FN) data (aneurysms detected on DSA but not detected on noninvasive imaging) were also obtained.

Statistical analysis
The data were analyzed using SAS 9.4 software (SAS version 9.4; SAS Institute, Cary, NC). Continuous variables were expressed as a mean ± standard deviation. A paired t-test was used for the analysis of aneurysm size associated with FP findings on CTA/MRA. Fisher's exact test was used to investigate the location of FPs on noninvasive imaging. The inaccuracy of aneurysm detection on noninvasive imaging ("secondary" FNs and FPs) versus DSA was also analyzed using Fisher's exact test. Chi-square was used to determine the accuracy of detection of multiple aneurysms on noninvasive imaging versus DSA. A $P \leq 0.05$ was considered as statistically significant.

RESULTS

Statistical analysis per patient
Angiograms performed on 1395 patients over a period of 3.5 years were retrospectively reviewed. A total of 286 patients with CTA ($n = 120$) or MRA ($n = 171$) imaging were included; 7 patients had both studies performed, but with 2 patients having a negative CTA and positive MRA - only the imaging showing a positive finding was included in the analysis. Aneurysm size on CTA was available in 85 patients and on MRA in 110 patients. These patients harbored a total of 317 aneurysms visualized on CT, MRA, or both. Average age was 56.8 years ± 13.4 (range 3–89 years). About 74.8% were female (214/286). Average age did not differ between females (56.8 years ± 13.1, range 3–80 years) and males (56.9 years ± 14.3, range 12–89 years).

When compared with the aneurysms detected on CTA/MRA, DSA showed negative results in 43 patients leading to a pooled FP rate of 15% on noninvasive imaging. FP rate on MRA was 13% (22/171) and on CTA was 18% (22/120) [Tables 1 and 2].

There were 31 symptomatic patients with a mean aneurysm size on DSA of 17.8 ± 11.3 mm (range 3–50 mm). Incidental aneurysms had a significantly smaller mean size of 7.7 ± 4.3 mm ($P < 0.001$). Symptoms included ophthalmoplegia (16 patients), cranial nerve III palsy (7 patients), other compression symptoms (5 patients), and embolic transient ischemic

Table 1: Magnetic resonance angiography versus digital subtraction angiography false positive

DSA	MRA positive
DSA positive	149
	87%
DSA negative	22 (FP)
	13%
Total	171

Analysis per patient. MRA: Magnetic resonance angiography, DSA: Digital subtraction angiography, FP: False positive

Table 2: Computed tomography angiography versus digital subtraction angiography aneurysm detection

DSA	CTA positive
DSA positive	98
	82%
DSA negative	22 (FP)
	18%
Total	120

Analysis per patient. DSA: Digital subtraction angiography, FP: False positive, CTA: Computed tomography angiography

attacks (TIAs) (3 patients).

About 95% (19/20) of patients with a family history of intracranial aneurysm or subarachnoid hemorrhage (SAH) were found to have an aneurysm on DSA, which was not significantly different than the 84% (224/266) of patients without a family history (*P* = 0.19). Mean aneurysm size on DSA in patients with a family history of aneurysmal SAH was 6.2 ± 6.7 mm, as compared to 9.2 ± 3.8 mm in patients with a negative family history.

No location was significantly susceptible to false detection of aneurysms on noninvasive imaging. Anterior versus posterior circulation location was not significantly associated with FPs (*P* = 0.133). In addition, DSA detected more multiple aneurysms than noninvasive imaging (*P* = 0.0001).

Statistical analysis per aneurysm

The FP rate of aneurysms detected by MRA was 16% (30/192) and the "secondary" FN rate (aneurysms detected on DSA and not detected on MRA) was 23% (48/210) [Table 3]. The inaccuracy (both FP and "secondary" FN) of aneurysm detection on MRA versus DSA was significant (*P* = 0.0008). CTA FP was 18% (22/125) and the FN for CTA was 31% (46/149) [Table 4]. The inaccuracy (FP and "secondary" FN) of aneurysms detected on CTA versus DSA was also significant (*P* = 0.0037).

Table 3: Magnetic resonance angiography versus digital subtraction angiography false positive and "secondary" false negative

DSA negative	MRA		
	Positive	**Negative**	**Total**
DSA positive	162	48 (FN)	210
	84%	23%	
DSA negative	30 (FP)	-	30
	16%	-	
Total	192	48	240

Analysis per aneurysm. MRA: Magnetic resonance angiography, DSA: Digital subtraction angiography, FP: False positive, FN: False negative

Table 4: Computed tomography angiography versus digital subtraction angiography false positive and "secondary" false negative

DSA	CTA		
	Positive	**Negative**	**Total**
DSA positive	103	46 (FN)	149
	82%	31%	
DSA negative	22 (FP)	1	23
	18%	-	
Total	125	47	172

Analysis per aneurysm. DSA: Digital subtraction angiography, FP: False positive, CTA: Computed tomography angiography, FN: False negative

The mean size of aneurysms detected on MRA and confirmed on DSA was 9.0 ± 7.0 mm. MRA FP increased significantly for aneurysms ≤ 3.5 mm (*P* < 0.0001). The mean size of aneurysms detected on CTA and confirmed on DSA was 7.9 ± 5.2 mm. CTA FP increased significantly for aneurysms ≤4.0 mm (*P* = 0.01).

DISCUSSION

The sensitivity and specificity of noninvasive CTA/MRA imaging in the detection of UIA have been previously described in the literature.[3,5,8,10-14,17-19] This data is variable and sometimes even contradictory as a result of varied quality of noninvasive imaging. An earlier meta-analysis reported that the accuracy of CTA/MRA is about 90%.[19] In a more recent meta-analysis, the specificity of MRA varied widely between 80% and 95%.[12] MRA FP is reportedly even higher, up to 38%,[13] and CTA FP up to 20.5%.[11] However, there have been technological advances in both CTA and MRA with reports of excellent sensitivity and specificity data.[8,17] Despite these improvements, newer noninvasive imaging modalities are not yet widely available and may be associated with higher costs. We examined the incidence of FP findings in a current real world setting.

In our study, we found that MRA and CTA FP were 13% and 18%, respectively. We also found that MRA FP increased significantly for aneurysms smaller than 3.5 mm (*P* < 0.001) and that CTA FP increased significantly for aneurysms smaller than 4.0 mm (*P* = 0.01). These results are consistent with previous reports of decreased accuracy in the detection of UIA <5 mm by both MRA and CTA.[11,13] A small UIA was defined in the first International Study of Unruptured Intracranial Aneurysms (ISUIA) study (retrospective group) as <10 mm, and in the second ISUIA trial (prospective group) as <7 mm.[16,20] The Japanese trial UCAS defined a small UIA as 5 mm or less.[15] Although ISUIA reported a virtually absent risk of rupture of small aneurysms in the anterior circulation, subsequent literature has shown that ruptured aneurysms encountered in common practice were often small.[2,6,9] Size ratio and other features besides absolute size were also found to be associated with ruptured small aneurysms,[6] and growth is known to be an important risk factor for hemorrhage.[1] Consequently, regardless of whether or not a small aneurysm should be treated, follow-up imaging must be recommended. Since serial imaging of small UIA is important, knowledge of CTA/MRA FP for small aneurysms is imperative.

Our data suggest that DSA does have a diagnostic role for small aneurysms. While DSA is considered as the gold standard for detecting and imaging UIA, it remains an invasive procedure. The risk of DSA is generally reported to be 1–2%.[7,21] However, this estimate reflects the risk in the entire population of

patients undergoing DSA who often present with, and are therefore predisposed to, TIAs and ischemic strokes. Indeed, in another meta-analysis, the combined risk of permanent and transient neurological complications associated with DSA in a population presenting with aneurysms and arteriovenous malformations without SAH was 0.3%, while the risk of permanent neurologic complications was 0%.[4] The benefit of detecting an FP finding with DSA would be the elimination of the need for further follow-up, as well as alleviating the negative psychological and economic effects associated with the diagnosis of an aneurysm.

Analysis of our data per aneurysm yielded similar results to our analysis per patient, with FP of 16% on MRA and 18% on CTA and a "secondary" FN of 23% and 31%, respectively. Given our study design, FN could not be determined directly from the data, but we defined "secondary" FN as UIA detected on DSA that were not detected on noninvasive imaging.

Not surprisingly, we found that the accuracy of noninvasive imaging modalities increases for larger aneurysms, especially when symptomatic. Aneurysm size was significantly larger among symptomatic versus asymptomatic patients in our cohort (17.8 mm vs. 7.7 mm, $P < 0.001$). Although symptomatic aneurysms were significantly larger, small aneurysms in critical locations can be symptomatic, such as the 3 mm posterior communicating artery aneurysm in one of our patients who presented with a cranial nerve III palsy. The role of DSA for large aneurysms remains primarily adjunctive rather than diagnostic, providing more detailed morphologic characteristics to guide surgical or endovascular treatment approaches.

Limitations

The primary limitation of this study is the potential for selection bias, given that not all patients with aneurysms detected on noninvasive imaging at our institution underwent confirmatory DSA. As such, it is possible that those selected to undergo DSA may have more frequently been cases where the presence of an aneurysm was already under question, thus, leading to a higher apparent rate of FP findings. Thus, the true rate of FP may be over estimated in our analysis. Another shortcoming of this study is its retrospective design; measures of sensitivity and specificity could not be obtained directly from the data given that we only included patients with positive CTA or MRA findings. However, our primary focus was to determine the rate with which positive noninvasive imaging may be misleading rather than to determine sensitivity rates. We did attempt to address this aspect by examining "secondary" FN in patients with multiple aneurysms. Most noninvasive scans in our study were performed at outside facilities employing variable techniques,

thereby possibly compromising the homogeneity and comparability of our data. At the same time, however, our results address the real world concern of patients referred from other facilities with small UIA detected on noninvasive imaging and provide insight to help guide the management of these patients.

CONCLUSION

DSA detection of FP UIA diagnosed on noninvasive imaging is significantly higher for aneurysms <4.0 mm. Accurate diagnosis with DSA may eliminate the need for further follow-up and its associated negative psychological and economic effects. Within the limitations of this retrospective study, we conclude that DSA has a diagnostic role in small aneurysms detected on noninvasive imaging.

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Conflicts of interest
There are no conflicts of interest.

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