Computed Tomography Angiography Spot Sign Does Not Predict Case Fatality in Aneurysmal Subarachnoid Hemorrhage With Intraparenchymal Extension

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Abstract

Background and Purpose—Many patients with aneurysmal subarachnoid hemorrhage (SAH) with intraparenchymal extension develop early hematoma expansion, which is not explained by aneurysmal rerupture in half of cases. In patients with primary intracerebral hemorrhage, the computed tomography angiography (CTA) spot sign predicts hematoma expansion and poor outcome. We conducted a 2-center prospective cohort study to evaluate whether CTA spot sign predicts case fatality in aneurysmal subarachnoid hemorrhage with intraparenchymal extension.

Methods—We studied consecutive patients with aneurysmal subarachnoid hemorrhage with intraparenchymal extension. Two experienced readers, blinded to clinical data, analyzed CTAs for spot sign presence. We assessed the proportion of patients with the CTA spot sign and tested its association with in-hospital and 90-day case fatality, using univariable and multivariable logistic regression.

Results—In 32 of 236 patients (14%), we found at least 1 spot sign. Acute surgical hematoma evacuation with aneurysm occlusion occurred in 120 patients (51%). The overall in-hospital case fatality rate was 37%. The CTA spot sign was not associated with in-hospital (multivariable odds ratio, 0.51 [95% confidence interval, 0.06–3.26]) or 90-day (multivariable odds ratio, 0.59 [0.21–1.65]) case fatality.

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Conclusions—The found frequency of CTA spot signs is lower after aneurysmal than primary intracerebral hemorrhage and is not associated with in-hospital or 90-day case fatality in patients with aneurysmal subarachnoid hemorrhage with intraparenchymal extension.

Keywords

CTA spot sign; in-hospital death; intracerebral hemorrhage; subarachnoid hemorrhage

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A neurysmal subarachnoid hemorrhage (SAH) is associated with high morbidity and case fatality. [1] Twenty per- cent of patients develop intraparenchymal extension of the hemorrhage, which is associated with worse outcome.[2] In addition, many patients develop expansion of the parenchymal hematoma in the initial 48 hours after aneurysmal rupture, but this can be attributed to rerupture of their aneurysms in only half of patients.[3]

The mechanism for hematoma expansion in the remaining patients is unclear but might be similar to that involved in expansion in primary intracerebral hemorrhage (ICH). In such patients, expansion of the hematoma is an important predictor of poor outcome.[4,5] During recent years, contrast extravasation following computed tomography angiography (CTA), termed the spot sign, has been shown to be an important and independent predictor of both hematoma expansion and poor clinical outcome (Figure).[6–9] The presence of a CTA spot sign marks those patients at highest risk for hematoma expansion, and may, therefore, provide a similar marker in patients with aneurysmal SAH with intraparenchymal extension.

The aim of this study was to assess the occurrence of a CTA spot sign in patients with ICH from aneurysmal rupture and to assess whether the spot sign is a predictor of poor outcome, as it is in patients with primary ICH. We, therefore, conducted a 2-center study to assess the prevalence and predictive value of the CTA spot sign in those patients.

Methods

Study Design

We studied prospectively collected data from 2 consecutive series of patients with aneurysmal SAH and ICH: 1 at Massachusetts General Hospital Boston and 1 at University Medical Center Utrecht, Utrecht, The Netherlands. The Institutional Review Boards of both hospitals approved all parts of this study. Data sharing between the 2 centers occurred without patient identifiers, and informed consent was obtained from all study participants or their legally authorized health-care proxies.

Study Subjects

Between January 2000 (Massachusetts General Hospital) or December 2003 (University Medical Center Utrecht) and December 2011 (both centers), consecutive patients presenting with an ICH, with or without SAH, from a ruptured aneurysm were screened for eligibility. Eligibility criteria included (1) diagnosis of ICH on baseline CT; (2) diagnosis of a ruptured aneurysm on CTA, conventional angiogram, or MR angiography; and (3) availability of a baseline CTA for spot sign reading. Exclusion criteria included the presence of any other suspected cause of secondary ICH (eg, vascular malformation, traumatic ICH, brain neoplasm, or hemorrhagic transformation of an ischemic stroke). Patients with primary, nonaneurysmal ICH were also excluded from this analysis.

Clinical Data

Clinical information was collected through patient interviews (or their surrogates) and extracted from their medical records. The data collected included age, sex, previous medical

history (including cardiovascular risk factors), and medications (including antiplatelet therapy and use of oral anticoagulants). Other collected variables were admission Glasgow Coma Scale (GCS) score, mean arterial blood pressure, and time from symptom onset to initial CTA. Three-month modified Rankin Scale (mRS) assessments were performed either in-person or via telephone, by trained and blinded study staff, to assess death and functional outcome. Poor functional outcome was defined as modified Rankin Scale >2.

CT Analysis

The diagnosis of a ruptured aneurysm was made based on the previously mentioned imaging modalities, by trained neuroradiologists at each center. Baseline parenchymal ICH and intraventricular hemorrhage volumes were assessed using Analyze 9.0 (Mayo Clinic, Rochester, MN) and Alice (PAREXEL International Corporation) software, according to previously published methods with high inter-rater reliability (κ=0.99).[6,10,11] Follow-up hematoma volumes, and thus hematoma expansion, were not assessed in this analysis because of the high rate (51%) of hematoma evacuation before follow-up imaging. Two experienced readers (H.B.B. and D.B.), blinded to clinical data, analyzed CTAs for presence, number, size, and attenuation (in Hounsfield Units) of spot signs, according to a previously described methodology with an almost perfect inter-rater agreement (κ=0.91).[10] Spot signs had to be present within the intraparenchymal hematoma but spatially distinct from the aneurysm (Figure).

Statistical Analysis

Discrete variables are presented as count and percentage (%) and continuous variables as mean and SD, or as median and interquartile range when appropriate. We tested the potential role of the CTA spot sign as predictor of poor functional outcome and in-hospital and 90-day death using univariable and multivariable logistic regression. The spot sign was analyzed as a dichotomized variable (absent or present). Multivariable models included age, sex, and variables with a P value of <0.20 in the univariable analysis. Collinear variables (measured using the variance inflation factor) were removed from the multivariable model when appropriate. Subsequently, we calculated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, as well as the C-statistic, using standard methods to assess the accuracy of the spot sign in predicting death and poor functional outcome. The threshold of significance was set at $P<0.05$. All statistical analyses were performed using JMP Pro version 9.0 (SAS Institute Inc, Cary, NC).

Results

Study Population

After applying the aforementioned inclusion and exclusion criteria, 236 patients remained eligible and consented for the current study. The overall consent rate for the study was >95%. Massachusetts General Hospital and University Medical Center Utrecht contributed 99 patients (42%) and 137 patients (58%), respectively. Cohort characteristics and characteristics stratified by spot sign status are shown in Table 1. In summary, mean age in the combined cohort was 56 (SD 14) years, 178 patients (75%) were females, and median GCS on presentation to the emergency department was 11 (inter-quartile range, 5–14). Acute interventions were common: 120 patients (51%) underwent surgical hematoma evacuation with aneurysm occlusion and 69 patients (29%) were treated with aneurysm coiling.

CT Imaging

At least 1 spot sign was observed in 32 patients (14%). Within the group of spot sign–positive patients, 74% had 1 spot sign, 21% had 2 spot signs, and 5% had >2 spot signs. Median ICH volume at baseline CT was 25 mL (interquartile range, 11–46), and median time to initial imaging was 10 hours (interquartile range, 3–18). Spot sign–positive patients had larger baseline ICH volumes and shorter times to imaging ($P<0.05$; Table 1).

Predictors of In-Hospital Death

The overall in-hospital case fatality rate was 37%. Age ($P=0.0001$), GCS ($P<0.0001$), baseline ICH volume ($P=0.01$), and baseline intraventricular hemorrhage volume ($P=0.005$) were associated with in-hospital death in univariable analysis (Table 2). Subsequently, these covariates remained independent predictors of in-hospital death in multivariable logistic regression (Table 3). Of note, GCS was not included in the multivariate analysis of in-hospital death because of strong collinearity with baseline ICH volume and better model performance with the inclusion of baseline ICH volume. The spot sign was not associated with in-hospital death in either univariable or multivariable analysis (when forced into the multivariable model).

Predictors of 90-Day Death and Poor Functional Outcome

At 90 days, 61% of patients within the combined cohort had died. Age ($P<0.0001$) and a history of hypertension ($P=0.02$) were associated with case fatality at 90 days in univariable analysis (Table 2). In multivariable analysis, only age ($P=0.0002$) remained significant after adjusting for potential confounders (Table 3). As for in-hospital death, we found no association between the spot sign and the 90-day death.

Of the patients who were still alive at 3 months, 133 patients (80%) were functionally dependent. In both univariable and multivariable analyses (adjusted for the same covariables as the analysis assessing death at 90 days, plus GCS on admission), the CTA spot sign was not associated with poor functional outcome: univariable odds ratio, 0.68 (95% confidence interval [CI], 0.23–1.99) and multivariate odds ratio, 0.93 (95% CI, 0.09–7.61).

Accuracy Measures

In this 2-center cohort, the spot sign had a sensitivity of 0.13, specificity of 0.86, positive predictive value of 0.35, negative predictive value of 0.62, and an overall accuracy of 0.59 for predicting in-hospital death. For 90-day death, the spot sign had a sensitivity of 0.13, a specificity of 0.83, a positive predictive value of 0.55, a negative predictive value of 0.38, and an accuracy of 0.41.

The C-statistic for the multivariable model of in-hospital death was 0.77 without the spot sign. When introducing the spot sign, the C-statistic only marginally increased to 0.79 (nonsignificant). The multivariable model for 90-day death had a C-statistic of 0.74 without the spot sign, and the C-statistic remained the same when including the spot sign in the model.

Discussion

In this study, we show that CTA spot signs are present in patients with aneurysmal SAH with intraparenchymal extension. In our series, a spot sign was present in 1 of 7 patients, which is lower than the proportion of ≈30% in patients with primary ICH.[8,9] In contrast to its strong association with poor functional outcome and death in primary ICH, spot sign presence was not associated with functional outcome or death in patients with aneurysmal SAH with intraparenchymal extension.

The only other study assessing the role of the spot sign in aneurysmal SAH included all secondary causes of ICH (not just ICH caused by ruptured aneurysms).[12] In that study, the spot sign was associated with in-hospital death in univariable analysis, but not in multivariable analysis. The proportions of patients with a spot sign were similar in both studies.[12] Of note, there is no overlap in patients between the current analysis and the referenced paper.

Multiple factors may contribute to the fact that the CTA spot sign predicts outcome in primary ICH, but not in aneurysmal SAH with intraparenchymal extension. Early hematoma evacuation was much more frequent (51%) in our series than it is in patients with primary ICH. Thus, hematoma enlargement and, therefore, higher risk of poor outcome might have been prevented in spot sign–positive patients who underwent early hematoma removal. It is likely that larger hematomas, which are associated with spot sign presence, have been evacuated more often than smaller ones, causing confounding by indication. Another factor is the average later scan time of patients having aneurysmal SAH with intraparenchymal extension compared with patients having primary ICH (median 10 versus 2 hours in the PREDICT [Prediction of Haematoma Growth and Outcome in Patients with Intracerebral Haemorrhage Using the CT Angiography Spot Sign] study),[8] which may as well account in part for the loss in sensitivity.[13]

Another possibility is that the mechanisms of ongoing bleeding are so different between aneurysmal and primary ICH that the CTA spot sign marks a completely separate process in these patients. When considering Fisher's model model of hematoma expansion in primary ICH (termed the avalanche model), expansion occurs because of the rupture of neighboring vessels around the initial hematoma, leading to additional bleeding and expansion of the hematoma.[14] With the intraparenchymal hemorrhage occurring in the vicinity of the subarachnoid space rather than more deep in the brain parenchyma, the continued bleeding, as represented by the spot sign, may cause more subarachnoid blood instead of additional blood in the brain parenchyma. This increase in subarachnoid blood may not lead to worse outcome, whereas increase in ICH volume in the parenchyma does. An alternative explanation could be the state of the underlying small vessels in SAH versus primary ICH. A recent genetic association study showed the apolipoprotein E ε2 allele to be associated with hematoma expansion, probably because of small vessel fragility caused by amyloid deposition.[15] Perhaps small vessels are differently affected in aneurysmal SAH compared with primary ICH, involving different pathways leading to final hematoma volumes. Further studies are warranted to answer this pathophysiological hypothesis.

A limitation of our study is the lack of follow-up CTs to assess hematoma expansion. However, because of the high rate of acute hematoma evacuation in patients with ICH from aneurysmal rupture, follow-up CTs in those patients are not usable for volumetric measurements to assess hematoma expansion. Another limitation is the relatively high missing rate of 3-month follow-up data.

Although in our study the CTA spot sign was not associated with in-hospital and 90-day case fatality, it does not mean the presence of the CTA spot sign can be ignored given the potential confounding by indication generated by early surgical interventions in this study. Further studies should focus on patients with a CTA spot sign who are currently not treated with emergency hematoma evacuation. If, in this subset of patients, hematoma enlargement occurs often and negatively influences outcome, such patients may benefit from earlier hematoma removal.

Acknowledgments

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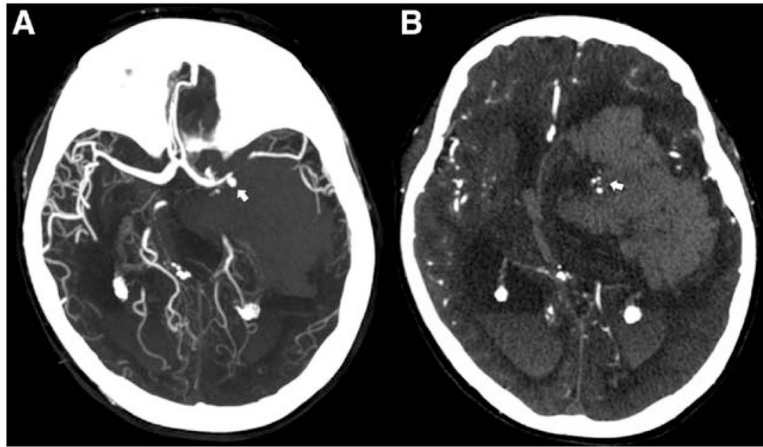
Figure.
Computed tomography angiography (CTA) of aneurysmal subarachnoid hemorrhage (SAH) with intraparenchymal extension and multiple spot signs. Acute CTA of a 57-year-old patient showing an aneurysmal SAH with intraparenchymal extension. **A**, The reformatted CTA shows a left middle cerebral artery aneurysm, as indicated by the arrow. **B**, The CTA source images demonstrate a large (150 mL) left hemispheric intracerebral hemorrhage with multiple spot signs within the inferomedial aspect of the hematoma (arrow).

Table 1

Cohort Characteristics

Variable	All Patients n (%)	Spot Sign–Negative Patients n (%)	Spot Sign–Positive Patients n (%)
No. of subjects	236	204 (86)	32 (14)
MGH	99 (42)		
UMCU	137 (58)		
Age (mean, SD)	56 (14)	55 (14)	57 (15)
Sex (female)	178 (75)	154 (75)	24 (75)
Hypertension	82 (35)	67 (33)	15 (47)
Diabetes	6 (4)	2 (2)	4 (21)
Atrial fibrillation	2 (1)	1 (1)	1 (5)
Congestive heart failure	5 (4)	3 (3)	2 (11)
Antiplatelets	28 (12)	21 (10)	7 (22)
Oral anticoagulants	2 (2)	2 (2)	0 (0)
GCS (median, IQR)	11 (5–14)	10 (5–14)	11 (5–14)
MABP (median, IQR)	106 (92–118)	103 (92–117)	109 (96–125)
Time to CTA, h (median, IQR)	10 (3–18)	11 (4–20)	5 (2–14)
CTA spot sign	32 (14)	n/a	n/a
Baseline ICH volume, mL (median, IQR)	25 (11–46)	23 (10–43)	36 (17–49)
Intraventricular extension	55 (23)	43 (21)	12 (38)
Baseline IVH volume, mL (median, IQR)	2 (0–19)	1 (0–13)	16 (7–51)
Intervention			
Clipping	120 (51)	105 (51)	15 (47)
Coiling	69 (29)	55 (27)	14 (44)
In-hospital death	87 (37)	76 (38)	11 (35)
90-day death	101 (61)	86 (62)	15 (55)
Poor outcome at 90 days (mRS>2)	133 (80)	116 (81)	17 (71)

CTA indicates computed tomography angiography; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IQR, interquartile range; IVH, intraventricular hemorrhage; MABP, mean arterial blood pressure; MGH, Massachusetts General Hospital; mRS, modified Rankin Scale; n/a, not applicable; and UMCU, Utrecht University Medical Center.

Table 2

Univariable Analysis of In-Hospital and 90-Day Death

Variable	In-Hospital Death		90-Day Death	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	1.04 (1.02–1.06)	0.0001	1.06 (1.03–1.10)	<0.0001
Sex (male)	0.77 (0.41–1.43)	0.44	1.10 (0.49–2.47)	0.84
Hypertension	1.68 (0.96–2.94)	0.09	2.44 (1.17–5.09)	0.02
Antiplatelets	1.60 (0.72–3.55)	0.30	2.38 (0.74–7.71)	0.19
GCS	1.27 (1.16–1.40)	<0.0001	1.07 (0.89–1.24)	0.23
MABP	1.01 (1.00–1.02)	0.17	1.01 (0.99–1.03)	0.33
Time to CTA	1.00 (0.98–1.03)	0.78	1.01 (0.98–1.04)	0.62
Baseline ICH volume	1.02 (1.01–1.04)	0.01	1.02 (0.99–1.06)	0.23
Baseline IVH volume	1.03 (1.01–1.05)	0.005	1.02 (0.98–1.06)	0.41
CTA spot sign	0.91 (0.41–2.01)	0.82	0.74 (0.30–1.85)	0.64

CI indicates confidence interval; CTA, computed tomography angiography; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MABP, mean arterial blood pressure; and OR, odds ratio.

Table 3

Multivariable Analysis of In-Hospital and 90-Day Death

Variable[*]	In-Hospital Death		90-Day Death	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	1.05 (1.01–1.12)	0.049	1.06 (1.03–1.10)	0.0002
Sex (male)	0.74 (0.13–3.56)	0.71	1.33 (0.56–3.28)	0.52
Hypertension	0.47 (0.11–1.86)	0.29	1.77 (0.78–4.11)	0.18
Antiplatelets	n/a	…	1.19 (0.33–5.04)	0.80
MABP	1.02 (0.99–1.04)	0.19	n/a	…
Baseline ICH volume	1.03 (1.01–1.06)	0.02	n/a	…
Baseline IVH volume	1.04 (1.01–1.07)	0.04	n/a	…
CTA spot sign	0.51 (0.06–3.26)	0.49	0.59 (0.21–1.65)	0.31

CI indicates confidence interval; CTA, computed tomography angiography; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MABP, mean arterial blood pressure; n/a, not applicable; and OR, odds ratio.

[*] Glasgow Coma Scale was not included in the multivariate analysis of in-hospital death because of strong collinearity with baseline ICH volume and better model performance with the inclusion of baseline ICH volume.