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Hemorrhage Recurrence Risk Factors In Cerebral Amyloid Angiopathy: Comparative Analysis of the Overall Small Vessel Disease Severity score versus Individual Neuroimaging markers

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Abstract

Introduction—An MRI-based score of total small vessel disease burden (CAA-SVD-Score) in cerebral amyloid angiopathy (CAA) has been demonstrated to correlate with severity of pathologic changes. Evidence suggests that CAA-related intracerebral hemorrhage (ICH) recurrence risk is associated with specific disease imaging manifestations rather than overall severity. We compared the correlation between the CAA-SVD-Score with the risk of recurrent CAA-related lobar ICH versus the predictive role of each of its components.

Methods—Consecutive patients with CAA-related ICH from a single-center prospective cohort were analyzed. Radiological markers of CAA related SVD damage were quantified and categorized according to the CAA-SVD-Score (0–6 points).

Subjects were followed prospectively for recurrent symptomatic ICH. Adjusted Cox proportional hazards models were used to investigate associations between the CAA-SVD-Score as well as each of the individual MRI signatures of CAA and the risk of recurrent ICH.

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Results—In 229 CAA patients with ICH, a total of 56 recurrent ICH events occurred during a median follow-up of 2.8 years [IQR 0.9–5.4 years, 781 person-years). Higher CAA-SVD-Score (HR=1.26 per additional point, 95%CI [1.04–1.52], p=0.015) and older age were independently associated with higher ICH recurrence risk. Analysis of individual markers of CAA showed that CAA-SVD-Score findings were due to the independent effect of disseminated superficial siderosis (HR for disseminated cSS vs none: 2.89, 95%CI [1.47–5.5], p=0.002) and high degree of perivascular spaces enlargement (RR=3.50–95%CI [1.04–21], p=0.042).

Conclusion—In lobar CAA-ICH patients, higher CAA-SVD-Score does predict recurrent ICH. Amongst individual elements of the score, superficial siderosis and dilated perivascular spaces are the only markers independently associated with ICH recurrence, contributing to the evidence for distinct CAA phenotypes singled out by neuro-imaging manifestations.

Keywords

Intracerebral hemorrhage; MRI; All Cerebrovascular Disease/Stroke; Cerebral Amyloid Angiopathy; Cerebral Small Vessel Disease

Introduction

The total MRI-based burden of small vessel disease (SVD) in cerebral amyloid angiopathy (CAA) has been recently correlated with severity of cerebrovascular pathology in an MRI-pathological cohort.¹ However, its clinical relevance in CAA-related outcomes remains unknown.

Of key clinical relevance, intracerebral hemorrhage (ICH) recurrence in CAA results to a considerable morbidity and mortality and its predictors are yet to be fully understood.² Recently, specific CAA neuroimaging markers, most notably cortical superficial siderosis (cSS), have been shown to be independently associated with higher odds of ICH recurrence.^{3–5} Reports published before the recognition of cSS as a key hemorrhage signature in CAA, have also suggested that cerebral microbleeds (CMBs)⁶ as well as white matter hyperintensities (WMH) of presumed vascular origin⁷ were positively associated with risk of recurrent events in lobar ICH patients. In this context, converging body of evidence indicates that the various neuroimaging expressions of CAA may in fact be indicators for different disease phenotypes with varying risk for ICH incidence or recurrence.^{8,9} Yet, no study has examined the relative importance of each of these markers versus the total burden of CAA-related SVD in assessing the risk of recurrent ICH.

We therefore conducted a retrospective study to investigate whether the total burden of SVD as assessed by the recently introduced CAA-SVD-Score was correlated with risk of recurrent lobar ICH and assessed comparatively the relative importance of each of its neuroimaging components.

Patients and Methods

Standard protocol approvals, registrations, and patient consents

This study was performed with approval of our local institutional review board.

Study population

Prospectively collected data from a longitudinal cohort of consecutive patients admitted at the Massachusetts General Hospital with spontaneous symptomatic lobar ICH between January 1994 and December 2012 were analyzed. Patients with strictly lobar hemorrhages (including CMBs and ICH) were prospectively categorized into the classic Boston criteria for definite, probable, or possible CAA. See Supplemental Figure 1 for patients' selection detail. Demographics, medical history and medications at baseline were prospectively obtained through in-person interviews (with the patient or surrogate) as previously described.¹¹

Neuroimaging acquisition and analysis

Detailed imaging acquisition and interpretation protocols are displayed in eAppendix 1. Briefly, neuroimaging markers of small vessel disease were evaluated on 1.5T MRI sequences according to STRIVE criteria¹¹ by blinded trained raters using validated scales.

As previously defined,¹ each marker (CMBs, cSS, CSO-PVS, and Fazekas WMH) was then categorized according to the 0–6 point CAA-SVD-Score as follows (points assigned for each category in brackets):

CMBs count: 2–4 [1] or 5 [2];

cSS: Focal [1] or Disseminated [2];

Centrum Semi-Ovale visible Perivascular Spaces (CSO-PVS): 20 [1];

WMH: scoring 3 for periventricular and/or scoring more than 2 for deep WMH on the Fazekas scale [1].

Follow-up data

Patients who survived the first 30 days after their index event and consented to the longitudinal study were followed for future recurrent lobar ICH. All patients were followed from their enrollment date until the occurrence of ICH, death, or the end of follow-up.² See eAppendix 2 for detail. Information on antithrombotic medication use during the follow-up period was also recorded where available.

Statistics

Survival time was calculated from date of baseline MRI scan until the date of first recurrence. Data were censored at the time of death from any cause other than documented symptomatic ICH. Univariable Cox-regression models were used to calculate unadjusted hazard ratio (HR) for the risk of ICH recurrence using the CAA-SVD-Score (analyzed both as an ordinal and continuous variable) as the independent variable. These analyses were then repeated separately using the CAA-SVD-Score's individual neuroimaging components adjusting for other potential predictors of recurrence (including age, gender, hypertension, dyslipidemia, diabetes and history of prior ICH).

Variables associated with significant association with ICH recurrence ($p < 0.1$) in univariate analyses were used in multivariate, fully adjusted Cox-regression models.

All tests of significance were two-tailed. Statistical analyses were performed with JMP Pro 12 (SAS Institute Inc. 2015. JMP® Pro 12. Cary, NC: SAS Institute Inc) software, a p-value of <0.05 was considered statistically significant.

The manuscript was prepared with reference to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.¹²

Results

Our final cohort included 229 CAA-related ICH survivors (4 with pathology definite CAA, 12 with CAA with supportive pathology, 124 with probable and 89 with possible CAA). Flowchart of patients' selection is presented in Supplemental Figure 1. Demographic and imaging characteristics of the study population are presented in Table 1. The overall median [IQR] SVD burden summary score was 2 [IQR: 1–3].

A total of 56 recurrent ICH occurred during a median follow-up of 2.8 years [IQR 0.9–5.4 years, 781 person-years, 5 years recurrence rate 28% –22 to 35-). Higher CAA-SVD-Score as well as older age, absence of diabetes, absence of history of hypertension, disseminated cSS, high degree of CSO-PVS and higher WMH were associated with higher unadjusted hazard ratios of recurrent ICH. (Table 2)

Higher CAA-SVD-Score (HR=1.26 per additional point, 95%CI [1.04–1.52], p=0.015) and older age remained independently associated with ICH recurrence risk in a multivariable Cox model adjusted for hypertension and diabetes (Table 3).

In a similar model, using the individual neuroimaging markers of CAA instead of the CAA-SVD-Score (Table 3), higher risk of recurrent ICH was independently associated with disseminated cSS (HR for disseminated cSS vs none, 2.89 95%CI [1.47–5.5], p=0.002 and for disseminated cSS vs focal cSS, 2.91–95%CI [1.31–6.6], p=0.008), high degree of CSO-PVS (HR=3.5–95%CI[1.04–21], p=0.042) as well as older age (HR=1.21, 95% CI [1.05–1.41], p=0.003 per 5 year increase).

In a sensitivity analysis, restricting the sample to the 140 patients with probable or definite CAA we found that a higher CAA-SVD-Score was not associated with an decrease in time until ICH recurrence (HR=1.06, 95% CI [0.84–1.33], p=0.603). cSS and frequent CSO-PVS remained the only independent neuroimaging markers of the risk of recurrent ICH with effects size of similar magnitude (See eTable 1 | Supplemental material)

Discussion

In this study we showed that (1) the total burden of SVD, assessed by the CAA-SVD-Score was (inconsistently) associated with a higher risk of ICH recurrence and (2) that this correlation was largely related to the influence of disseminated cSS and high-degree of CSO PVS. Neither CMBs nor WMH had any significant association with the risk of ICH recurrence in this cohort of patients with CAA. Our results suggest that specific CAA imaging characteristics, rather than the overall severity of SVD burden, are responsible for higher risk of recurrence in CAA patients with ICH.

The concept of a total SVD Score was first introduced in ischemic stroke patients,¹³ and adapted for CAA in a recent study that demonstrated a direct correlation between CAA-SVD-Score and underlying pathological severity. Here we found that while independently associated with ICH recurrence in the overall CAA cohort, a higher SVD burden summary score (i.e. more severe CAA pathologically) was not as strongly related to the risk of recurrent ICH as cSS and/or CSO-PVS (HR=1.26 per additional point, 95%CI [1.04–1.52], p=0.015 vs 2.89, 95%CI [1.47–5.5], p=0.002 for disseminated cSS and HR=3.5, 95%CI [1.04–21], p=0.042 for frequent CSO-PVS). Further, when restricting the analysis to probable and definite CAA patient subgroup, we found that the association between CAA-SVD-Score and ICH recurrence risk was not sustained, while cSS and frequent CSO-PVS remained strongly and independently associated.

Our results add to previous studies^{3–5} suggesting that cSS is an independent and strong risk factor for ICH recurrence in patients with CAA, and suggests that a specific neuroimaging profile, rather than the overall burden of SVD related damage is of importance when managing patients after a CAA-related ICH. cSS is hypothesized to result from repeated episodes of bleeding in the subarachnoid spaces, by fragile leptomeningeal and superficial cortical vessels damaged by vascular amyloid deposition.

Our study also showed an independent and novel association between higher degrees of enlarged CSO-PVS and ICH recurrence. Dilated PVS have been implicated as early markers of SVD,¹⁴ but their association with the risk of ICH recurrence is largely unexplored.¹⁵ In a recent pathologic study, areas of enlarged CSO-PVS appear to be spatially associated with areas of more severe CAA which may be due to failure of drainage of interstitial fluid resulting from deposition of beta-amyloid in cortical and leptomeningeal arteries.¹⁶ The strong association of cSS with CSO-PVS in the current study may be the neuroimaging manifestation of the above-described pathologic observation. It is conceivable that the presence of both markers substantially increases risk of vessel rupture and ICH, but the underlying mechanism remains poorly understood. However, the important association between cSS and higher degree of CSO-PVS as well as the synergistic effect of those findings on the risk of subsequent bleeding (HR=8.16, 95%CI [2.21–53], p=0.007) in our study may help to identify a high risk ‘bleeding prone’ imaging profile in CAA patients. Longitudinal imaging studies exploring the sequential evolution of both markers are needed and this finding awaits confirmation in an external cohort. Overall, our results suggest that a specific disease phenotype (e.g. a more hemorrhage prone or active one), rather than the overall disease burden, better identifies CAA patients with highest risk of ICH recurrence.

Our study has limitations. The single-center design could limit the generalizability of our findings. However, as our study represents one of the largest cohorts of patients with CAA with extensive follow-up, this bias may be limited. Also, we were not able to account for blood-pressure variation as a cause for ICH recurrence in our analyses during the follow-up period¹⁷ which could influence our final results. However, the main purpose of this study was to determine the clinical utility of a SVD burden score in comparison to individual neuroimaging markers in CAA rather than to identify all independent predictors of ICH recurrence. Finally, since severe dilated CSO-PVS was a highly prevalent finding in our

sample, the spread of the estimates regarding associations with risk of recurrence was wide, lowering the precision of this finding.

In conclusion, in CAA patients with lobar ICH, while the total burden of SVD (as measured by the CAA-SVD-Score) is (unsteadily) associated with recurrent ICH, this effect appears to be related to the influence of disseminated cSS and high-degree of CSO-PVS. These findings add to our understanding of the neuroimaging profile of CAA and its relationship to clinical outcome and strengthen evidence for CAA phenotypes with varying risk of ICH recurrence. External validation in even larger well-phenotyped cohorts will be useful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Cerebral Amyloid Angiopathy hemorrhage recurrence-risk is unsteadily related to overall disease burden
- Cortical superficial siderosis is the strongest marker of hemorrhage recurrence risk
- Dilated perivascular spaces may also mark patients at higher risk of hemorrhage recurrence
- Overall severity is not as strongly associated with hemorrhage recurrence than those markers

Table 1

Baseline characteristics of study population

Variable	Value [*]
Total	n=229
Age at event	73 ± 10.7
Female Gender	121 (53%)
History of ICH	36 (16%)
Hypertension	145 (63%)
Diabetes	27 (12%)
Dyslipidemia	102 (44%)
MRI markers of SVD severity	
Total SVD Score	2 [1–3]
Cerebral Microbleeds count	
[0–1]	153 (67%)
[2–4]	32 (14%)
5	44 (19%)
Superficial Siderosis	
Focal	49 (21%)
Disseminated	36 (16%)
Enlarged CSO-PVS	
[0–19]	35 (16%)
20	194 (84%)
Qualifying WMH ^a	134 (59%)

^{*} Variables are displayed as absolute number (% of total), or Mean ± Standard Deviation or Median [25th–75th percentiles] as appropriate.

^a Qualifying WMH, scoring 3 for periventricular and/or scoring 3 for deep WMH on the Fazekas scale.

Abbreviation: SVD, Small Vessel Disease. CAA-SVD-Score, CAA SVD Burden Score, CSO-PVS, Centrum semi-ovale Perivascular spaces. WMH, White matter hyperintensity.

Table 2

Univariable associations with ICH recurrence.

Variable	HR	95% CI	p-value
Age at Event [†]	1.30	1.14–1.51	<0.001
Female gender	0.98	0.57–1.66	0.926
Prior Intracerebral Hemorrhage	1.31	0.69–2.36	0.391
Hypertension	0.58	0.34–0.99	0.045
Diabetes Mellitus	0.4	0.05–1.01	0.053
Dyslipidemia	1.01	0.59–1.73	0.962
CAA-SVD-Score (3 vs <3)	1.78	1.05–3.06	0.033
CAA-SVD-Score [†]	1.33	1.11–1.59	0.002
Cortical Superficial Siderosis			
<i>Disseminated vs None</i>	3.45	1.79–6.46	<0.001
<i>Disseminated vs Focal</i>	2.95	1.37–6.49	0.006
Enlarged CSO-PVS (20)	4.8	1.49–29.3	0.005
Cerebral Microbleeds count			
<i>5 vs [0–1]</i>	0.96	0.46–1.84	0.896
<i>5 vs [2–4]</i>	0.59	0.26–1.36	0.215
Qualifying WMH *	1.72	1–3.06	0.049
Total Cerebral Microbleeds [†]	1	0.99–1.1	0.2
WMH volume (cc) [†]	1	0.99–1.02	0.37

* Qualifying WMH, scoring 3 for periventricular and/or scoring more than 2 for deep WMH on the Fazekas scale.

[†] Continuous variables, HR is per point increase in regressor except for age (HR per 5 years increase).

Abbreviation: SVD, Small Vessel Disease. CAA-SVD-Score, CAA SVD Burden Score, CSO-PVS, Centrum semi-ovale Perivascular spaces. WMH, White matter hyperintensity.

Table 3

Proportional hazards regression for time until ICH recurrence.

Variable	HR	95% CI	p-value
Model 1			
Age at Event[†]	1.23	1.07–1.50	0.003
Hypertension	0.61	0.35–1.05	0.075
Diabetes Mellitus	0.46	0.07–1.51	0.225
CAA-SVD-Score[†]	1.26	1.04–1.52	0.015
Model 2			
Age at Event[†]	1.21	1.05–1.41	0.003
Hypertension	0.63	0.35–1.09	0.103
Diabetes Mellitus	0.60	0.09–1.95	0.420
Cortical Superficial Siderosis			
<i>Disseminated vs None</i>	2.89	1.47–5.5	0.002
<i>Disseminated vs Focal</i>	2.91	1.31–6.6	0.008
Enlarged CSO-PVS (20)	3.50	1.04–21	0.042
Qualifying WMH [*]	1.39	0.78–2.60	0.256
Cerebral Microbleeds count			
<i>5 vs [0–1]</i>	0.84	0.39–1.67	0.640
<i>5 vs [2–4]</i>	0.69	0.29–1.65	0.397
Model 3			
cSS and CSO PVS [3 vs 0]	8.16	2.21–53	0.007

Model 1: Analysis of the CAA-SVD-Score, All variables displayed.

Model 2: Analysis of each of the CAA-SVD-Score components. All variables in the model displayed.

Model 3: All variables of Model 2 except cSS and CSO-PVS scores merged into a single ordinal variable

^{*} Qualifying WMH, e.g. scoring 1 point in the CAA-SVD-Score (that is, patients scoring 3 for periventricular and/or scoring more than 2 for deep WMH on the Fazekas scale)

[†] Continuous variables, RR is per 5 years increase in regressor.

Abbreviation: SVD, Small Vessel Disease. CAA-SVD-Score, CAA SVD Burden Score, CSO-PVS, Centrum semi-ovale Perivascular spaces. WMH, White matter hyperintensity.