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Intracranial atherosclerosis and cerebral small vessel disease in intracerebral hemorrhage patients☆

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ABSTRACT

Background: The association between cerebral small vessel diseases (cSVD) and intracranial atherosclerosis is debated and conflicting results have been reported. We sought to investigate this association in patients with intracerebral hemorrhage (ICH), due to severe cSVD.

Methods: Consecutive ICH patients were divided into those meeting criteria for cerebral amyloid angiopathy (CAA) and those with deep hypertensive ICH consistent with hypertensive cSVD (HTN-SVD). White matter hyperintensity volumes (WMH) and microbleed counts (MB) were measured on MRI. CTA was rated for severity of intracranial carotid calcifications and for presence of >50% intracranial stenosis (ICS). Associations of intracranial atherosclerosis severity with type of SVD (CAA vs HTN-cSVD) and with imaging and clinical markers of cSVD burden were analyzed.

Results: The cohort included 253 CAA and 90 HTN-SVD patients. In multivariable models, the type of cSVD (CAA vs. HTN-cSVD) was not associated with calcification severity (OR = 1.04, 95% CI [0.62–3.5], p = 0.37) or presence of ICS (OR = 0.84, 95% CI [0.21–2.74], p = 0.78).

We found no association between intracranial atherosclerosis (calcifications and stenoses) and parenchymal markers of cSVD severity (WMH and MB, adjusted p ≥ 0.2 for all comparisons) and no association with presence of dementia before ICH (adjusted p ≥ 0.2 for both comparisons).

Conclusions: We found no association between intracranial atherosclerosis and parenchymal or clinical consequences of cSVD, suggesting that cSVDs while sharing some risk factors are not influenced by upstream larger vessel pathologies.

1. Introduction

Intracranial carotid artery calcifications (ICACs) [1] have been suggested to be associated with cerebral small vessel disease (cSVD) severity [2,3] and cognitive manifestations in patient cohorts with dementia or ischemic stroke as well as in population based-studies [4–6]. Intracranial arterial stenoses (ICS), another consequence of atherosclerotic changes, can similarly be readily diagnosed on head Computed Tomography Angiography (CTA) but their significance is not well-understood outside of ischemic stroke research.

The effects of shared risk factors between cSVD and intracranial atherosclerosis and our imperfect ability to measure other potential confounders make it difficult to disentangle these associations. Some risk factors such as hypertension affect both large and small vessels whereas others like hyperlipidemia and diabetes may preferentially harm the larger vessels [7].

☆ **Authors and individual contribution to the manuscript**
Gregoire Boulouis: project design, imaging analysis, data analysis, write up
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A recent study showed that markers of "arterial aging" were associated with Alzheimer's pathology in older individuals independent of atherosclerosis [8]. Overall, the interrelationship between cSVD and large vessel pathologies at large is still unclear [9–12].

Sporadic cerebral amyloid angiopathy (CAA) and hypertensive arteriopathy (HTN-cSVD) are the two most common and severe forms of cSVD in older adults [13], both responsible for spontaneous intracerebral hemorrhage (ICH) which remains a riveting public health concern [14,15].

Multiple lines of evidence suggest that CAA and HTN-cSVD are also independent contributors to cognitive impairment in older adults [16–18]. A cohort of patients with cSVD severe enough to cause ICH provides a high yield setting to study the interrelationships between intracranial atherosclerosis and cerebral cSVD.

ICACs have demonstrated to be fairly reliable proxies for intracranial atherosclerosis and independent risk factors for cerebrovascular ischemic events [1,6,19–23]. However, to date, the relationship between ICACs and cSVD in intracerebral hemorrhage (ICH) patients is not elucidated. Atherosclerotic intracranial stenosis is an important etiology of ischemic strokes. Its treatment typically involves antithrombotics which are known to increase risk of ICH in patients with cSVD [24]. Understanding the prevalence of ICS in a cohort of patients with cSVD-related ICH is also important as aggressive lowering of blood pressures is commonly performed in these patients without knowledge of such data, despite long-standing concerns for ischemic consequences in this setting.

1.1. Aims

In a large cohort of ICH patients, we investigated the frequency and risk factors of intracranial large artery disease and tested the hypothesis that intracranial large artery disease (ICLAD) was associated with the type of cSVD and presence of dementia before ICH.

2. Patients and methods

2.1. Study population and data collection

We have analyzed prospectively collected data from 545 consecutive patients admitted at the Massachusetts General Hospital (MGH) with primary symptomatic ICH [15] and enrolled in an ongoing cohort study between January 2000 and February 2012 as extensively described in previous publications [25,26]. Based on review of neuroimaging (MRI) and clinical data, patients were divided into those with strictly lobar Hemorrhages (including MB and ICH) meeting Boston criteria for definite, probable, or possible CAA, [27] eventually addressed as "CAA" and those with strictly deep supratentorial or brainstem Hemorrhages consistent with HTN-cSVD. The current analysis was restricted to patients who had a head CT-angiography within 3 months of the ICH.

2.2. Clinical data

Subject enrollment, clinical data collection and MRI acquisition were performed as described previously [25,26]. In brief, the following clinical variables were systematically recorded for each subject: age, sex, presence of hypertension, diabetes, hypercholesterolemia, previous history of ICH and antithrombotic drug use at baseline.

2.3. Standard protocol approvals, registrations, and patient consents

This study was approved by the hospital institutional review board.

2.4. Neuroimaging acquisition and analysis

Whole brain MRI images were obtained using a 1.5 Tesla MR scanner (GE Sigma) and included T2-weighted, T2*-weighted gradient-recalled echo (T2*-GRE; repetition time/echo time [TR/TE] 750/50 ms, 5 mm slice thickness, 1 mm inter-slice gap) and fluid attenuated inversion recovery (FLAIR; TR/TE 10000/140 ms, inversion time 2200 ms, 1 number of excitations, 5 mm slice thickness, 1 mm inter-slice gap).

Total WMH volumes of CAA and HTN-cSVD-related ICH were quantitatively measured on FLAIR MRI, using a two-step planimetric semi-automated segmentation as previously described [28]. MB presence and number were evaluated on axial blood-sensitive MR images according to current consensus criteria [29,30] and categorized as lobar (i.e. cortical-subcortical) or deep (i.e. basal ganglia, thalami, brainstem).

Enlarged Perivascular Spaces (EPVS) were assessed in line with the STRIVE recommendations; [30] basal ganglia (BG) and centrum semiovale (CSO), using a validated 4-point visual rating scale (0 = no EPVS, 1 ≤ 10 EPVS, 2 = 11–20 EPVS, 3 = 21–40 EPVS and 4 ≥ 40 EPVS). We pre-specified a dichotomized classification of EPVS status as high (score >2) or low (score ≤2) in line with previous studies [31].

Baseline head CTAs were acquired as part of routine protocols 25 s after an 80 cm^3 bolus of iodine contrast and reconstructed at 1.25 mm thickness with 0.6 mm spacing. All imaging analyses were performed blinded to clinical information, and CTAs reviewed blinded to MRI data.

ICACs were rated at the level of cavernous carotids accounting for extent (0–4 points) and thickness (0–4 points) of calcifications, according to a previously reported scale [6] (see Fig. 1). Because no difference was found between carotid arteries in any of the patients, scores from both ICAs were added yielding a total 16-point scale. A total score of 1–6 was considered to be mild, and a score above 7 (upper tertile), moderate to severe.

The degree of intracranial stenosis was evaluated using the NASCET method as appropriate (Fig. 2).

2.5. Statistics

Clinical and neuroimaging characteristics of CAA versus HTN-cSVD-related ICH patients were compared in univariate analyses, using 2-sample *t*-test, Wilcoxon rank sum, Pearson's χ-square and Fisher exact tests as appropriate. Multivariable logistic/ordinal regression analyses were performed to look for independent associations of underlying cSVD type with presence/severity of ICACs, adjusting for age, gender, vascular risk-factors, total WMH volume, lobar MBs, deep MBs, high CSO-EPVS grade and high BG-EPVS grade. Stepwise backward variable selection ($p > 0.05$) was used to generate a minimal adjusted model. Logarithmic transformation was used for variables with a right skewed distribution, to be entered in regression models when needed. Significance level was set at 0.05 for all analyses. SPSS Software was used for all analyses. The manuscript was prepared with reference to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [27].

3. Results

3.1. General characteristics

Among 545 patients screened for eligibility, 113 were excluded for the absence of CTA within 90 days and 85 for other reasons including mixed location bleeds [see patients' selection flowchart in online supplement eFigure 1].

Our final study population therefore included 253 CAA-ICH patients (5 pathology-proven, 15 probable with supportive pathology, 130 probable and 103 possible CAA according to the Boston criteria [27]) and 90 HTN-cSVD related ICH. Demographic and imaging characteristics of the study population are presented in Table 1. CAA patients were older (mean age 73.5 vs. 64.8, $p < 0.001$), more of female gender, with less hypertension and Diabetes Mellitus, demonstrating a higher WMH burden, more severe/frequent CSO EPVS and less frequent/severe BG EPVS than HTN-cSVD cases in univariable analyses (See Table 1).