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Enlarged perivascular spaces in the basal ganglia are independently associated with intracranial atherosclerosis in the elderly

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ABSTRACT

Background and aims: Enlarged basal ganglia perivascular spaces (BG-PVS) are a marker of cerebral small vessel disease (SVD). The association between enlarged BG-PVS and atherosclerosis has been explored, but knowledge is limited to extracranial vessels. We aimed to assess whether enlarged BG-PVS correlate with carotid siphon calcifications (CSC), used as a surrogate of intracranial atherosclerosis.
Methods: Atahualpa residents aged ≥60 years underwent head computed tomography (CT) for assessment of CSC, and brain magnetic resonance imaging (MRI) for evaluation of BG-PVS and other imaging markers of SVD. We evaluated the association between BG-PVS and CSC severity (dependent variable) using regression models adjusted for demographics and cardiovascular risk factors.
Results: Of 437 candidates, 354 (81%) were included. Grade 1 CSC were observed in 131 (37%), Grade 2 in 99 (28%), Grade 3 in 92 (26%), and Grade 4 in 32 (9%) subjects. MRI showed >10 enlarged BG-PVS in 97 (27%) participants, moderate-to-severe white matter hyperintensities in 81 (23%), lacunar infarcts in 39 (11%), and deep microbleeds in 28 (8%). Fully-adjusted models showed a significant association between enlarged BG-PVS and CSC severity. Individuals with Grade 4 CSC have 3 times de odds of having enlarged BG-PVS than those with Grade 1 CSC. Enlarged BG-PVS were observed in 20% *versus* 41% of individuals with Grade 1 and Grade 4 CSC, respectively.
Conclusions: Enlarged BG-PVS often coexist with CSC, suggesting that a common pathogenetic mechanism may explain the occurrence of both conditions.

1. Introduction

Perivascular spaces (PVS) are interstitial fluid-filled cavities surrounding small penetrating intracranial vessels, which are involved in physiological mechanisms of brain fluid and metabolic waste clearance [1]. These normal structures – which are most often located in the basal ganglia (BG) and centrum semiovale (CSO) – are not often seen on MRI unless they are dilated. While exact pathogenetic mechanisms involved in PVS dilatation are still elusive, studies have shown different correlates for enlarged PVS according to their anatomic distribution, suggesting several processes involved in their occurrence [2]. For example, a prospective cohort study showed that enlarged CSO-PVS are associated with cerebral amyloid angiopathy and superficial siderosis [3]. On the contrary, recent evidence links the presence of enlarged BG-PVS with neuroimaging markers of cerebral small vessel disease (SVD) [4–6]. In addition, enlarged BG-PVS have been associated with brain atrophy, microvascular damage of other organs, and even with inflammatory conditions, suggesting that the spectrum of correlates of enlarged BG-PVS is not confined to SVD markers [7–9]. The association between enlarged BG-PVS and atherosclerosis has also been explored, but knowledge on this relationship is limited to extracranial vessels [10–12]. Being carotid siphon calcifications (CSC) a neuroimaging surrogate of intracranial atherosclerosis, it is plausible to find an association between CSC and enlarged BG-PVS, which may help understand pathogenetic mechanisms implicated in their occurrence. In a previous study, we demonstrated that older adults with high calcium content in the carotid siphon have increased odds of having white matter hyperintensities (WMH) of presumed vascular origin and lacunar infarcts [13]. Here, we aimed to assess whether enlarged BG-PVS are associated with CSC, after adjusting for the other neuroimaging signatures of SVD.

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2. Materials and methods

2.1. Study population

Atahualpa is an isolated rural village of Coastal Ecuador that achieves several requisites to be considered an optimal setting for the practice of epidemiological studies. As described elsewhere [14], villagers are homogeneous regarding race/ethnicity, lifestyles, socio-economic status and diet. Atahualpa residents are natives with little evidence of cross-breeding. Almost all men belong to the blue-collar class and most women are homemakers. Diet is rich in oily fish and carbohydrates but poor in red meat and dairy products. These consistencies reduce the risk of unexpected confounders at the time of data analyses. The I.R.B. of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867) approved the study.

2.2. Study design

All Atahualpa residents aged ≥60 years enrolled in the Atahualpa Project were offered a non-enhanced CT scan of the head and a brain MRI at Hospital-Clínica Kennedy (Guayaquil), and consenting individuals with no contraindications for the practice of these exams were included in the present study. We evaluated whether enlarged BG-PVS were associated with severity of CSC, after adjusting for demographics, cardiovascular risk factors, and the other neuroimaging signatures of SVD.

2.3. Neuroimaging protocol

Neuroimaging exams were performed by the use of a Philips Brilliance 64 CT scanner and a Philips Intera 1.5T MRI scanner (Philips Medical Systems, Eindhoven, the Netherlands), following pre-defined protocols. In brief, slice thickness on CT was 3 mm with no gap between slices, and MRI included two-dimensional multislice turbo spin echo T1-weighted, fluid attenuated inversion recovery (FLAIR), T2-weighted, and gradient-echo sequences in the axial plane, as well as a T1-weighted sequence oriented in the sagittal plane; slice thickness was 5 mm with 1 mm gap between slices. All exams have been independently reviewed by a neurologist and a neuroradiologist, with adequate kappa coefficients for inter-rater agreement for lesions of interest [15–17].

CT digital images were viewed on the Osirix Medical Imaging software (Pixmeo, Geneva, Switzerland) using the bone window setting to identify and grade CSC. According to Woodcock et al. [18], Grade 1 CSC were defined as the absence or near-absence of calcification, Grade 2 as tiny scattered calcifications, Grade 3 as thick interrupted or thin confluent calcifications, and Grade 4 as thick contiguous calcifications.

MRIs were reviewed following research standards for cerebral SVD [19]. In particular, WMH of presumed vascular origin were defined as lesions appearing hyperintense on T2-weighted images that remained bright on FLAIR (without cavitation) and graded in none, mild, moderate and severe, according to the modified Fazekas scale [20]. Cerebral microbleeds (CMB) were identified and rated according to the microbleed anatomical rating scale [21]; for this study, only CMB located deep in the brain were considered. Lacunar infarcts were defined as fluid-filled cavities measuring 3-15 mm located in the territory of a perforating arteriole [19]. Enlarged BG-PVS were defined as small (<3 mm) structures of CSF intensity that followed the orientation of perforating arteries. Enlarged BG-PVS were classified according to their number in a single slice in one side of the brain (Fig. 1). As previously described, enlarged BG-PVS were rated as abnormal if > 10 of these lesions were present (grades 2, 3 and 4) [4].

2.4. Clinical covariates investigated

Demographics and cardiovascular risk factors were assessed through interviews and procedures previously described in the Atahualpa Project [22]. In brief, we used the American Heart Association criteria to assess smoking status, physical activity, diet, the body mass index, blood pressure, fasting glucose, and total cholesterol blood levels [23].

2.5. Statistical analysis

Data analyses are carried out by using STATA version 14 (College Station, TX, USA). In univariate analyses, continuous variables were compared by linear models and categorical variables by x^2 or Fisher exact test as appropriate. Using a logistic regression model, we evaluated whether enlarged BG-PVS (as the dependent variable) were associated with severity of CSC, after adjusting for demographics, cardiovascular risk factors, and the other markers of SVD. Thereafter, using CSC as the dependent variable, we evaluated whether enlarged BG-PVS were independently associated with the severity of CSC, after adjusting for the same confounders. In addition, we evaluated the proportion of individuals with enlarged BG-PVS according to the severity of CSC by the use of a probability model (Delta-method).

3. Results

Of 437 community-dwelling Atahualpa residents aged ≥60 years identified during door-to-door surveys, 363 (83%) underwent

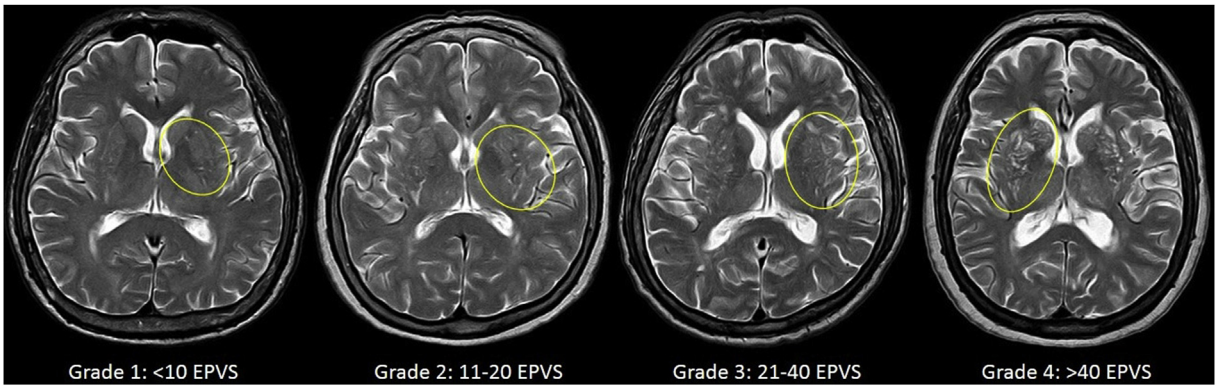

Fig. 1. T2-weighted MRI showing four degrees of enlarged basal ganglia perivascular spaces (circles).
Grades 2, 3 and 4 are considered abnormal.