Enlarged perivascular spaces and cognitive impairment after stroke and transient ischemic attack

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Background Previous studies suggested that enlarged perivascular spaces are neuroimaging markers of cerebral small vessel disease. However, it is not clear whether enlarged perivascular spaces are associated with cognitive impairment. We aimed to determine the cross-sectional relationship between enlarged perivascular spaces and small vessel disease, and to investigate the relationship between enlarged perivascular spaces and subsequent cognitive impairment in patients with recent cerebral ischemic event.

Methods Anonymized data were accessed from the virtual international stroke trial archive. We rated number of lacunes, white matter hyperintensities, brain atrophy, and enlarged perivascular spaces with validated scales on magnetic resonance brain images after the index stroke. We defined cognitive impairment as a mini mental state examination score of ≤26, recorded at one year post stroke. We examined the associations between enlarged perivascular spaces and clinical and imaging markers of small vessel disease at presentation and clinical evidence of cognitive impairment at one year using linear and logistic regression models.

Results We analyzed data on 430 patients with mean (±SD) age 64.7 (±12.7) years, 276 (64%) males. In linear regression analysis, age ($\beta = 0.24$; $p < 0.001$), hypertension ($\beta = 0.09$; $p = 0.025$), and deep white matter hyperintensities ($\beta = 0.31$; $p < 0.001$) were associated with enlarged perivascular spaces. In logistic regression analysis, basal ganglia enlarged perivascular spaces were independently associated with cognitive impairment at one year after adjusting for clinical confounders (OR = 1.72, 95% CI = 1.22–2.42) and for clinical and imaging confounders (OR = 1.54; 95% CI = 1.03–2.31).

Conclusions Our data show that in patients with ischemic cerebral events, enlarged perivascular spaces are cross-sectionally associated with age, hypertension, and white matter hyperintensities and suggest that enlarged perivascular spaces in the basal ganglia are associated with cognitive impairment after one year.

Introduction

Cerebral small vessel disease (SVD) affects small arteries, capillaries, and venules in the brain.1 The effect of SVD on both brain vessels and parenchyma encompasses a wide range of pathologic processes detectable by conventional neuroimaging such as magnetic resonance (MR) and computed tomography (CT). Traditionally, imaging features of SVD have included lacunes, white matter change, brain atrophy, and microbleeds.2 There is increasing evidence that enlarged perivascular spaces (EPVS) may be another imaging marker of SVD.3,4 Perivascular (Virchow-Robin) spaces are virtual fluid-filled spaces surrounding penetrating arterioles and venules which provide a drainage conduit for cerebral interstitial fluid. Normally undetectable with conventional imaging, they become more frequent with age. EPVS can be seen on T2-weighted MRI as punctate < 2 mm round (if vessel perpendicular to plane of image) or linear (if vessel in the plane of the image) cerebrospinal fluid (CSF-isointense) lesions along the course of penetrating arteries.

A recent study of 298 patients reported that EPVS were associated with risk factors for SVD (older age), also clinical manifestations of SVD (lacunar stroke subtype), and imaging manifestations of SVD (white matter lesions).4 However, there is scarce evidence regarding the effects of EPVS on cognitive status. In a hospital-based series of patients presenting with transient ischemic attack (TIA) or stroke, EPVS were not associated with cognitive performance in any of the cognitive domains investigated, although an association was seen between EPVS and other imaging markers of SVD.5

As these findings await external validation in other cohorts, we used clinical and imaging data from the virtual international stroke trials archive (VISTA)6 to address two complementary research questions: 1. What is the relationship between EPVS and clinical and imaging markers of SVD, and 2. What is the relationship of EPVS with post stroke cognitive function.

METHODS

We accessed patient level data from the VISTA resource and conducted retrospective analyses. We included patients with ischemic stroke and TIA and accompanying MR-based neuroimaging. Ethical approval was not required since data were anonymous.

Clinical variables of interest included age, sex, ethnicity, hypertension, diabetes, hypercholesterolemia, cigarette smoking at time of the index stroke, ischemic heart disease, atrial fibrillation, peripheral artery disease, depression. Functional status at time of the patient evaluation was assessed according to Oxford Handicap Scale (OHS).7 Definite diagnosis of either stroke or TIA was performed by single trial investigators on the basis of duration of symptoms and imaging presence of cerebral infarction. Stroke etiology has been previously classified according to Trial of Org 10172 (TOAST) classification8 on the basis of clinical and neuroimaging investigations. For the purposes of the present study, we did not cross-check the stroke etiology classifications and we relied on the investigators' subtyping. According to TOAST, small artery cerebral infarction was diagnosed when present: (a) retained consciousness and higher cerebral function; (b) CT or MR brain scan that was normal or showed a subcortical or brainstem small infarct; and either (c) a classical lacunar syndrome or a non-classical lacunar syndrome; (d) no evidence of either cardioembolism and ispilateral large vessel stenosis (>50%).

A neurologist trained in MR assessment and blinded to clinical data (FA) rated all the available scans (T1, T2, FLAIR sequences) for presence and severity of SVD features, according to STRIVE (STandards for ReportIng Vascular changes on nEuroimaging) recommendations.2 An experienced neuroradiologist (JMW) cross-checked a sample of the readings. Where the index infarct was too large to allow the rating of the SVD features, we performed the SVD ratings only in the non-affected hemisphere. We defined lacunes as round shaped cerebrospinal fluid isointense lesions measuring ≤20 mm in diameter on axial section in the white matter, basal ganglia or brainstem as seen on T1, T2 or FLAIR sequences. We graded white matter hyperintensities as 0–3 according to Fazekas scale in deep and periventricular white matter.9 Brain atrophy was defined as central and cortical, and rated separately with a three-point scale as none, mild-moderate and severe against a reference MR brain template with a previously used methodology.10 EPVS were defined as ≤2 mm round or linear cerebrospinal fluid isointense lesions (T2 hyperintense and T1/FLAIR hypointense). As previously done in similar studies,3⇓–5 we rated EPVS in basal ganglia and centrum semiovale using a 5-point ordinal scale11 as follows: 0 = no EPVS, 1 = 1–10 EPVS, 2 = 11 to 20, EPVS, 3 = 21 to 40 EPVS, and 4 = > 40 EPVS (Figure 1). We separately assessed EPVS in basal ganglia and centrum semiovale because they arise from perforating arteries from deep cerebral circulation (basal ganglia EPVS) and from pial cerebral circulation (centrum semiovale EPVS) and may therefore have different pathophysiologic processes.

Cognitive function at baseline was not recorded routinely in the index trial source and only data on presence of clinical diagnosis of dementia were available. For the purposes of the present study, we selected patients without dementia at baseline. Cognitive function one year after stroke was assessed using MMSE, and we defined cognitive impairment as a score of MMSE ≤ 26.12

Statistical analysis

We described general characteristics of the study population using basic descriptive statistics. We assessed correlation (using Spearman's rank correlation coefficient) between the site of the EPVS (basal ganglia and centrum semiovale) and other neuroimaging features of SVD (number of lacunes, ordinal gradings of white matter change and brain atrophy).

Total EPVS were normally distributed, so we examined associations between explanatory variables and total EPVS using linear regression. We also tested associations with total EPVS with logistic regression (none or mild total EPVS = 0–2 vs. moderate to severe total EPVS = 3–8). Basal ganglia and centrum semiovale EPVS were not normally distributed, and so we assessed univariate and multivariate associations with explanatory variables dichotomizing EPVS into 0–1 vs. 2–4, replicating the method used in previous studies.3,4 In both multivariate models, we included as explanatory variables age, sex, hypertension, diabetes, lacunar stroke (according to TOAST classification), periventricular, and deep white matter hyperintensities, central atrophy.

We described the distribution of MMSE according to number of EPVS in basal ganglia and centrum semiovale. MMSE values were skewed, we therefore analyzed differences within EPVS groups with Kruskal–Wallis test and preferred to use logistic regression rather than linear regression to present association data.

We described univariate associations between imaging markers of SVD and cognitive impairment, and then created a multivariate logistic regression model exploring associations between each

imaging marker of SVD (included EPVS in basal ganglia and centrum semiovale) and MMSE, adjusting for age, sex, OHS at baseline, hypertension, diabetes, and depression.

In a second logistic regression model, we included additional explanatory variables of imaging SVD markers that were statistically significant ($p < 0.05$) in the first model, adjusting for the same clinical confounding factors.

Finally, in a third model, we repeated the second logistic regression model after combining central and cortical atrophy single scores (global cerebral atrophy).

Statistical analysis was carried out using SPSS for Windows (version 22.0; SPSS, Armonk NY, IBM Corp.).

RESULTS

A total of 430 patients with ischemic stroke or TIA had corresponding MR scans at baseline. Six scans were excluded from rating of any SVD marker due to poor image quality. EPVS rating was not possible in 17 scans because of movement artefact. Assessment of all imaging markers of SVD was therefore possible in 407 (95%) scans.

Mean age (±SD) of the study population was 64.7 (±12.7) years, 276 (64%) patients were male. Less than a half (47%) of the population was Caucasian. Median time to baseline assessment was 44 days (IQR = 8–101) after the index stroke event.

A total of 349 (81%) patients had ischemic stroke as qualifying event, of whom almost a half (48%) were lacunar subtype on TOAST criteria (Table 1). Included patients had modest levels of early post stroke disability with median OHS = 1 (IQR = 1–2) at baseline. The patients had a range of concomitant cardiovascular diseases, with hypertension being the most common (Table 1).

Median EPVS in the centrum semiovale was 2 (IQR = 1–2), median EPVS in basal ganglia 1 (IQR = 1–2). Compared to total and centrum semiovale EPVS, basal ganglia EPVS were generally more closely related to other imaging markers of SVD, with the strongest correlation for both periventricular and deep white matter hyperintensities ($\rho = 0.61$, $p < 0.001$). The weakest correlation was found between centrum semiovale EVPS and lacunes ($\rho = 0.25$, $p < 0.001$) (Table 2).

EPVS as neuroimaging feature of SVD

Our linear regression model showed that age ($\beta = 0.24$; $p < 0.001$), hypertension ($\beta = 0.09$; $p = 0.025$), and deep white matter hyperintensities ($\beta = 0.31$; $p < 0.001$) were independently associated with total EPVS. Logistic regression model confirmed such age (OR = 1.08; 95% CI = 1.05–1.11), hypertension (OR = 2.04; 95% CI = 1.17–3.57), and deep white matter hyperintensities (OR = 2.11; 95% CI = 1.24–3.58) associations. There was a non-statistically significant trend towards a significant association of EPVS score with lacunar strokes ($\beta = 0.08$; $p = 0.054$) according to TOAST classification, periventricular white matter hyperintensities ($\beta = 0.13$; $p = 0.087$), and cortical atrophy ($\beta = 0.10$; $p = 0.056$) (Table 3). Regarding location of EPVS, in logistic regression models centrum semiovale EPVS (OR = 2.58; 95% CI = 1.69–3.93), periventricular (OR = 2.31; 95% CI = 1.29–4.13), and deep (OR = 2.24; 95% CI = 1.29–3.89) white matter hyperintensities were independently associated with

basal ganglia EPVS; whereas age (OR = 1.05; 95% CI = 1.02–1.09), hypertension (OR = 2.00; 95% CI = 1.10–3.63), and basal ganglia EPVS (OR = 2.93; 95% CI = 1.78–4.81) were associated to centrum semiovale EPVS (Table 4).

EPVS and cognitive impairment

We identified 408 non-demented patients at baseline. Eight patients (2%) died within one year and 49 (12%) patients had no MMSE data recorded at follow up; therefore, a total of 351 (86% of those with appropriate MR imaging) patients had MMSE available one year after the qualifying event. In total 137 patients (39%) had cognitive impairment as defined by our threshold of MMSE ≤ 26. We described the groups with and without available MMSE data, there were no obvious between group differences (Supplemental Table).

MMSE scores differed according to number of EPVS, both in basal ganglia ($p < 0.001$) and in centrum semiovale ($p = 0.001$) (Figure 2).

In separate logistic regression models describing associations with dichotomized MMSE at one year, after adjusting for clinical features, we found that white matter hyperintensities (OR = 1.36, 95% CI = 1.07–1.73), cortical atrophy (OR = 2.42, 95% CI = 1.39–4.22), and basal ganglia EPVS (OR = 1.72, 95% CI = 1.22–2.42) were independently associated with MMSE ≤ 26, whereas centrum semiovale EPVS were not. Total EPVS number were not associated with cognitive impairment (OR = 1.18; 95% CI = 0.96–1.45). In further models where we included other statistically significant imaging markers of SVD, basal ganglia EPVS showed a consistent, strong association with cognitive impairment (OR = 1.59; 95% CI = 1.07–2.39). Also cortical atrophy (OR = 2.27; 95% CI = 1.25–4.11) and cerebral atrophy (OR = 1.48; 95% CI = 1.06–2.06) were associated with cognitive impairment, while white matter hyperintensities lost their association (OR = 1.01; 95% CI = 0.75–1.37) (Table 5).

DISCUSSION

We have confirmed that EPVS are consistently associated with clinical and imaging markers of SVD, such as age, hypertension and white matter changes. Our data add to the existing weight of evidence that EPVS are a imaging marker of SVD. We have found that in a population of patients with ischemic stroke and TIA, total EPVS were not associated with cognitive impairment, whereas EPVS in the basal ganglia were associated with cognitive impairment at one year.

Our results are broadly in agreement with previous studies that have described association of EPVS with increasing age2⇓–4 and hypertension,2,13 both important clinical risk factors for SVD. In contrast to previous studies on ischemic stroke patients,3,4 we did not find a significant association between lacunar stroke and EPVS but this likely reflects our use of a stroke subtype classification which is known to suffer from imprecision, with only moderate agreement among different physicians.14 Furthermore, the MR assessment was blinded to clinical features, and we did not cross-checked the TOAST etiological subtype with the imaging features of the index event. This potential imprecision may have reduced our ability to detect a lacunar etiological subtype-EPVS association.

Total EPVS showed significant associations with age, hypertension, and deep WMH. Interestingly, association between EPVS and SVD markers seemed to vary by location, with basal ganglia EPVS showing association with imaging markers of SVD, whereas centrum semiovale EPVS having stronger relation with clinical risk factors. However, the direction of the association was the same for both basal ganglia and centrum semiovale EPVS, although the latter was not statistically significant. A possible differential consequence of EPVS by location has been suggested by other groups,15 but we cannot draw any conclusion in this regard because of the cross-sectional design of the study.

Other groups have studied EPVS and cognition, albeit much of the literature relates to non-stroke cohorts.16,17 Although we found a lack of association between total EPVS and cognition, basal ganglia EPVS were significantly associated with cognitive status after one year. It seemed that basal ganglia rather than centrum semiovale EPVS had a clinical relevance with cognition, and the estimation of both parameters together provided as net effect a lack of association, even though the direction of the association was similar. A previous study describing EPVS and cognition in stroke did not find the significant association that we have described for basal ganglia EPVS.5 Compared to this study, we had access to a larger sample size and so had greater power to detect a modest association. A cross-sectional study reported a statistically significant correlation between basal ganglia EPVS and cognition in 189 patients (of whom 77 had lacunar stroke), but the correlation was not confirmed after adjustment for age.18 A possible explanation could be that location of EPVS has diverse effects on cognition, perhaps reflecting the different pathophysiology of deep (basal ganglia EPVS) and pial (centrum semiovale EPVS) circulation. Other groups previously advanced this hypothesis regarding the different role of EPVS according to their location. For example, centrum semiovale EPVS rather than basal ganglia EPVS seemed to be highly prevalent in patients with cerebral amyloid angiopathy, supporting the role of centrum semiovale EPVS as imaging marker in the diagnosis of the pathology.19,20

SVD is thought to be a key driver of vascular cognitive impairment and various imaging markers of SVD have been previously associated with cognitive deficits, particularly in executive function.1 For example, white matter changes have been associated with cognitive decline and dementia.21,22 A systematic review and meta-analysis suggested that cognitive impairment is common among patients with lacunar stroke,23 and clinically silent infarcts have been also associated with cognitive decline.24 Lobar microbleeds, detectable with T2* sequences are associated with executive function impairments.25 Our study suggests that EPVS, previously proposed as markers of SVD,3,4 could be added to the list of features to evaluate when investigating cognitive function. Interestingly, while we demonstrated that white matter changes were independently associated with cognition on crude analysis, after adjustment for basal ganglia EPVS and cerebral atrophy, white matter changes lost their association with cognition. In this regard, we could speculate that basal ganglia EPVS may represent a more important predictor of post stroke cognition than white matter hyperintensities.

Our study has limitations. The major limitation is the lack of a measure of cognitive status at baseline, since we only had data about presence or absence of clinically detected dementia. We were therefore unable to fully determine the causal relationship between EPVS and cognitive status at one year, rather we report an association that deserve further investigation with proper study design. We furthermore acknowledge that evaluation of cognitive deficits should be based on a comprehensive assessment including a complete multi-domain neuropsychological battery. As a brief cognitive screening tool, MMSE is not a substitute for formal neuropsychological and clinical

assessment, nor is particularly sensitive to the cognitive deficits seen in SVD. Nonetheless, MMSE is a feasible tool for detection of post stroke cognition status and is commonly used in practice as well as in research. Secondly, 15% of our study population had no available MMSE data. These missing data could bias results, although comparisons of the groups with and without MMSE data did not suggest fundamental differences in baseline characteristics. We acknowledge that stroke itself may affect cognitive status (i.e. up to a third of stroke survivors suffer from cognitive impairment), and we partly accounted for this adjusting for stroke severity at the time of the first clinical evaluation. Finally, EPVS can be found in different locations, and we did not rate EPVS in the hippocampus and brainstem, as some authors have previously suggested.26 Rather we chose to use a scale previously validated in patients with stroke and cerebral SVD.14

Strengths of our study include access to a large study population with robust data on EPVS and SVD in patients with ischemic stroke and TIA. We used a highly standardized methodology, replicating elements of previous studies in an independent cohort. Moreover, patients included in the VISTA resource are drawn from a number of international trials and our results represent patients from different ethnicity, with diverse cardiovascular risk factor profile.

In conclusion, we have confirmed that in patients with ischemic stroke or TIA, EPVS represent another neuroimaging feature of SVD, acknowledging that topographical distinctions in associations may occur between the site of EPVS and risk factors and imaging features of SVD. Even though total EPVS were not associated with cognitive impairment, we showed a meaningful association between EPVS in basal ganglia and cognitive impairment at one year after ischemic stroke or TIA. Since this is result of a retrospective analysis, it should be interpreted with caution and needs external validation, and our results are hypothesis generating only. This hypothesis deserves further research with proper study design. However, it may suggest that basal ganglia EPVS might be considered as unfavorable neuroimaging marker in studies that investigate cognitive function in patients with ischemic brain events, and should be assessed in studies investigating cognition. Together with evidence from studies in non-stroke patients, our results support the hypothesis that EPVS, particularly in basal ganglia, may have an important role in identifying patients at risk of cognitive impairment and dementia.

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