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Enlarged Perivascular Spaces in Basal Ganglia: A Potential Early Imaging Marker of Hypertension induced Cerebral Small Vessel Disease

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Abstract

Background: Cerebral Small vessel disease (cSVD) is a common cause of cognitive decline. In this study we aimed to ascertain if enlarged Perivascular spaces (ePVS) in basal ganglia are a potential independent biomarker of hypertension induced cSVD.

Methods: The study participants comprised of patients between 40 and 70 years of age referred for Brain MRI. Patients with hypertension ≥ eight years formed the case group. Non-hypertensive patients were selected as controls. Subjects with (i) carotid artery plaques, more than 50% stenosis of carotid artery on either side (ii) micro/macro haemorrhage and intra cranial atherosclerosis were excluded. 2D FLAIR sequence was used for rating of white matter hyperintesities (WMH) and differentiating lacunar infarcts from enlarged PVS. A 3D FIESTA C was acquired to clearly delineate PVS. Sensitivity, specificity, PPV, NPV and AUC of PVS and WMH for predicting lacunar infarct was calculated in overall study subjects.

Results: 61 hypertensives and 59 non-hypertensives, fulfilled the eligibility criteria. Lacunar infarct was present in 22 (36.07%) hypertensives. WMH was present in 13 (21.31%) cases and six (10.17%) controls. ePVS was seen in 56 (91.80%) cases and 13 (22.03%) controls. There was 100% sensitivity of ePVS in predicting lacunar infarct among hypertensives. The AUC of ePVS in predicting lacunar infarct was significantly more than that of WMH. In overall study subjects maximum AUC was seen in the 41 to 50 years age group.

Conclusion: Enlarged Peri vascular spaces should not simply be overlooked as an inevitable consequence of aging. ePVS in basal ganglia could be an early and independent marker of hypertension induced Cerebral Small Vessel Disease.

Key words: Enlarged Perivascular spaces, White Matter Hyperintensity, Cerebral Small Vessel Disease, Lacunar infarct.

Introduction

Due to mild clinical symptoms at the onset, cerebral small vessel disease (cSVD) is frequently a neglected cause of stroke. However, it remains one of the leading causes of cognitive decline in the elderly population[1,2]. As there is no consensus on clinical criteria for cSVD, neuroimaging has become an important diagnostic tool for both symptomatic and silent cSVD. Hypertension remains the commonest and most important risk factor for cSVD[1,4-6]. Peri vascular spaces (PVS) are interstitial fluid-filled spaces surrounding the penetrating vessels in the brain. Long-term hypertension can cause endothelial damage with altered blood brain barrier leading to leakage of plasma components into the vessel wall resulting in enlarged PVS (ePVS)[3,7]. Studies have shown that ePVS often co-exist with white matter hyper intensities (WMH) and lacunes, which are themselves associated with hypertension[2]. ePVS have only recently been recognised as a marker of cSVD. Lacunar infarcts have long been established as a clinical and imaging prototype of cSVD due to hypertension[8]. WMH of presumed vascular origin, have been considered the most widely accepted MRI marker of cSVD in our set up and hardly any data is available on PVS. In this study we aimed to ascertain if ePVS in basal ganglia could be a potential independent imaging marker of hypertension induced cSVD.

Material and Methods

Study design and eligibility

The study population comprised of patients between forty and seventy years of age, referred to the Radiology Department at our hospital for Brain MRI between August 2019 and Mar 2021. The study participants comprised of patients with a history of hypertension for eight or more years selected as cases, and patients in the same age group with no history of hypertension, selected as controls for this comparative cross sectional study. Relevant clinical and imaging data was obtained and recorded from all recruited

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participants. Hypertension was defined as repeated BP ≥ 140/90 mmHg or on antihypertensive medication[9].

Presence of other risk factors

Presence of diabetes, defined as Fasting Plasma Glucose ≥ 126 mg/dl or 2 hours Post-Prandial Plasma glucose ≥ 200 mg/dl or HbA1c ≥ 6.5%, was recorded[10].

Presence of dyslipidaemia was defined as per European Society of Cardiology and European Atherosclerosis Society guidelines[11].

Presence of history of smoking, elicited or volunteered, both current and past, irrespective of the form and frequency of smoking as was recorded.

Pre-imaging exclusion

Study participants with more than 50% carotid artery stenosis or carotid wall plaques on any side detected on Sono-Colour Doppler study/CT Angiography and ii) those with Atrial Fibrillation/valve prosthesis, which could be a likely source of cardiac emboli, were excluded.

Imaging procedure

After obtaining informed consent, brain image acquisition of all study participants was carried-out on 3 Tesla MR imaging scanner (Discovery 750; GE Healthcare, Milwaukee, Wisconsin) using a 32 channel phased array head coil. The essential sequences for all study participants included: 2D Axial T1W, 2D Axial T2W, 2D Axial T2 FLAIR, 2D Axial DWI, 2D Axial SWI and 3D TOF Angiography of Brain.

Post-imaging exclusion

Study participants showing previous or current macro/micro haemorrhages on SWI, more likely due to amyloidopathy were not included.

Study participants with atherosclerotic changes in MCA, seen as narrowing or stenosis on 3D TOF MR angiography were excluded[12].

MRI acquisition for WMH

FLAIR images were acquired using the same parameters for all study participants: T R 12,000 ms, TE 140 ms, TI 2,500 ms; flip angle 150 degree; slice thickness 4 mm; interslice gap 1 mm; FOV 210 x 210 mm; matrix 352 x 352; acquisition time 2 min 36 secs.

Lacunar infarcts were defined as infarcts ≥ 20 mm on axial section the territory of a single perforating artery. Number and location of lacunar infarcts was recorded. Recent lacunar infarcts were differentiated from previous infarcts on DWI imaging. Previous lacunar infarcts ≥ 15 mm, with CSF signal intensity on T1W and T2 W sequence and hyperintense rim on FLAIR sequence were defined as lacunes[13].

WMH scoring

Deep white matter hyperintensity, 13 mm or more from ventricular surface and within 4 mm from corticomedullary junction was recorded[14].

We used a simple modified Fazekas rating scale for grading WMH[15].

- Grade 0: WMH not visualised in the deep white matter.
- Grade 1: punctate lesions in the deep white matter with a maximum diameter of 9 mm for a single lesion and of 20 mm for grouped lesions.
- Grade 2: early confluent lesions of 10 - 20 mm single lesions and >20 mm grouped lesions in any diameter, and no more than connecting bridges between the individual lesions.
- Grade 3: single lesions or confluent areas of hyperintensity of ≥ 20 mm in any diameter.

WMH contiguous to the ventricular surface resulting from CSF leakage and irregular periventricular WMH likely due to haemodynamic insufficiency was excluded from the scoring.

MRI acquisition for peri-vascular spaces

For study participants with visualised PVS in Basal Ganglia seen on T2 W sequence an additional 3D Fast Imaging Employing Steady State Acquisition with Cycled Phases (Fiesta C) sequence was acquired using the following parameters: TR 8 ms; TE 2.4 ms; matrix 300 x 300, NEX 87, flip angle 55 degree, slice thickness 6 mm, inter slice gap. 2 mm. Slice per SLAB 120, Bandwidth 62.5 Khz, slice oversampling: 6.7, FOV 230 mm matrix 384 × 384, voxel size: 0.5 × 0.5 × 0.6 mm. Acquisition time 4 min 10 secs. To reduce scan time and motion artefacts, sections were limited to region of Basal ganglia.

PVS scoring

Peri vascular spaces was defined as round or linear fluid filled spaces with CSF signal intensity, that followed the typical course of the lateral striate arteries[13]. Number of ePVS was recorded at substantia innominata at the infraputaminal level, section of ventral putamen, and the dorsal putamen at level of caudate on the basis of scoring by Patankar *et al*[7], ePVS was rated as grade 0 to 3.

- Grade 0: five or less than five ePVS on either side in infraputaminal section.

- Grade 1: five or more than five ePVS on either side in infraputaminal section.
- Grade 2: five or more ePVS on either side in ventral putamen.
- Grade 3: five or more ePVS in either caudate.

Two raters (MKM and CP with ten and eight years experience in neuroimaging independently performed the scoring for lacunar infarcts,WMH and ePVS. Both raters repeated the scoring sessions with order of subjects changed to ensure reliability and reduce bias.

Statistical analysis

The following statistical tests were applied for the results:

1. The association of the variables which were quantitative in nature were analysed using Mann-Whitney Test.
2. The comparison of the variables which were qualitative in nature was analysed using Chi-Square test/Fisher's Exact test.
3. Sensitivity, specificity, positive predictive value and negative predictive value of PVS and WMH for predicting lacunar infarct was calculated.
4. Univariate logistic regression was used to find predictors of lacunar infarct. For statistical significance, p value of less than 0.05 was considered as significant.A weighted Cohen test was used to quantify the level of inter rater and intra rater agreement for lacunar infarcts, WMH and PVS. The values more than > .81 defined excellent agreement.

The study was conducted in accordance with guidelines of our hospital ethics committee.

Results

Sixty one hypertensive and 59 non-hypertensive patients (control group) fulfilled the inclusion criteria. The distribution of clinico-demographic characteristics of study subjects by age groups, gender and other risk factors is shown in Table I.

Score of Lacunar Infarcts, WMH and ePVS

Cohens' kappa value demonstrated excellent intra-rater agreement between the two scoring sessions for each rater for lacunar infarcts,WMH and ePVS.

Lacunar infarcts were noted in 22 (36.07%) hypertensive patients (p < .0001, Fisher Exact test). Most lacunar infarcts were noted in the thalamus and periventricular white matter. Cohens' kappa value for inter-rater agreement was .93 for lacunar infarct indicating excellent agreement between raters.

Table I: Comparison of Socio-demographic characteristics between cases and controls.

Socio-demographic characteristics	Case (n = 61)	Control (n = 59)	Total	p value	Test performed
Age (years)					
41 - 50	21 (34.43%)	19 (32.20%)	40 (33.33%)	0.943	Chi square test, 0.117
51 - 60	20 (32.79%)	21 (35.59%)	41 (34.17%)		
61 - 70	20 (32.79%)	19 (32.20%)	39 (32.50%)		
Mean ± SD	55.18 ± 8.49	55.95 ± 7.78	55.56 ± 8.12	0.667	Mann Whitney test; 1717.50
Median (IQR)	54 (48 - 63)	58 (48.5 - 62.5)	56 (48 - 63)		
Range	41 - 70	42 - 68	41 - 70		
Gender					
Female	12 (19.67%)	11 (18.64%)	23 (19.17%)	0.886	Chi square test, 0.02
Male	49 (80.33%)	48 (81.36%)	97 (80.83%)		

WMH was present in 13 (21.31%) cases and six (10.17%) controls (p = 0.095, chi square test). Among cases the WMH emerged and progressed in higher age groups. It was not seen in the 41 to 50 years age group. WMH was noted in two (10%) cases in the 51 to 60 years age group and 11 (55%) in the 61 to 70 years age group. (p < .0001, Fisher's Exact test). Grade 1 WMH was seen in two (10%) cases in the 51 to 60 years age group and four (20%) cases in the 61 to 70 years age group. Grade 2 WMH was seen in one (5%) case in the 51 to 60 years age group, three (15%) cases in the 61 to 70 years age group. Grade 3 WMH was seen in five (25%) cases in 60 to 70 years age group. Cohens' kappa value for inter-rater agreement was .89 for WMH, indicating excellent agreement.

Imaging characteristics of PVS on FIESTA-C

PVS in basal ganglia were clearly seen on 3D-FIESTA C (Fig. 1b, Fig. 2b). In the coronal plane, PVS were semi-curved tubular structures oriented upward initially and then curved medially to the floor of the lateral ventricle, following the course of the lateral striate arteries (Fig.1b). Striate arteries were noted within the larger PVS (Fig. 3a, 3b). Some PVS were irregular in shape and size with pencil-tip like configuration of tubules (Fig. 4a, 4c). Lacunar infarcts were clearly seen separate from the ePVS (Fig. 4b). The PVS were more prominent in the infra-putaminal section (Fig. 2c). Cohens' kappa value for interrater agreement was .87 for scoring of ePVS, indicating excellent agreement.

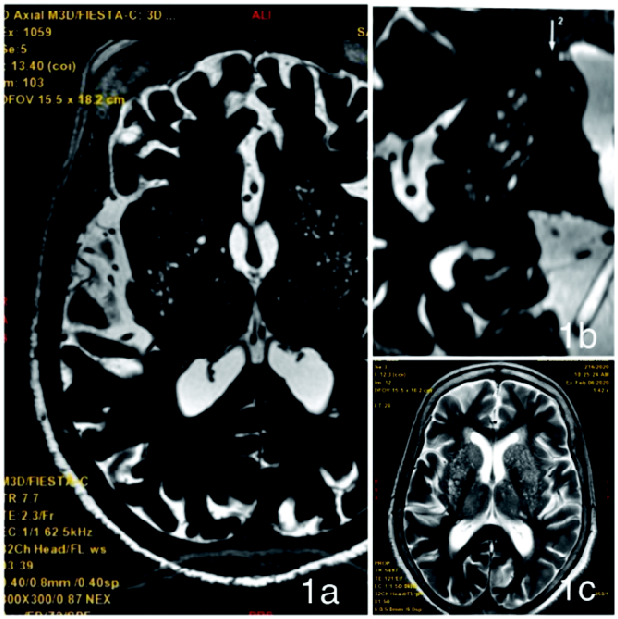

Fig. 1: *69-year-old male with hypertension, A. 3D Axial FIESTA-C image shows multiple ePVS in bilateral basal ganglia. (more than 5 spaces seen in right caudate scored as grade 3), B. 3D coronal FIESTA-C image shows multiple curvilinear spaces following the trajectory of lenticulostriate arteries. C. 3D axial image shows multiple ePVS in bilateral infraputaminal section.*

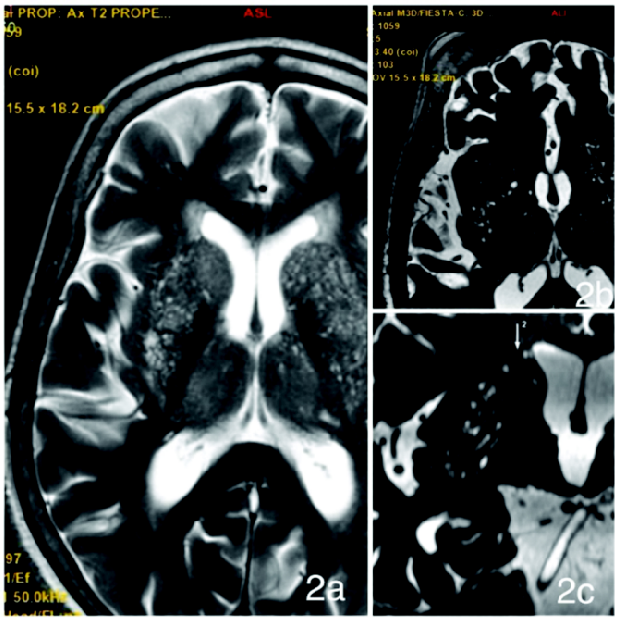

Fig. 2: *70-year-old female with history of hypertension, A. Axial T2 image shows multiple enlarged Perivascular spaces (ePVS) in basal ganglia with Swiss cheese striatum. The margins of PVS are blurred B. 3D Axial FIESTA-C image shows sharply delineated PVS C. 3D Coronal FIESTA-C image shows PVS following curvilinear path reaching up to right caudate (less than five ePVS in caudate scored as grade 2).*

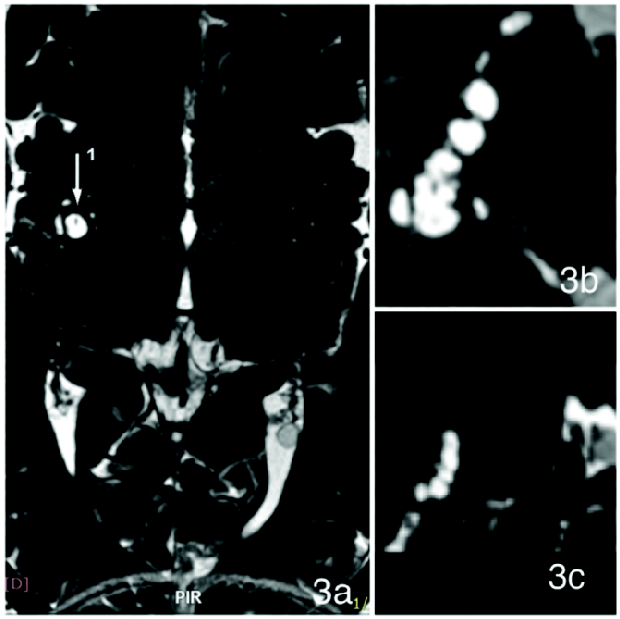

Fig. 3: *45-year-old male with hypertension, A. 3D Axial FIESTA-C image shows enlarged round ePVS with central dot (lenticulostriate artery) in right substantia innominata, B. 3D Coronal FIESTA-C image shows dilated beeded ePVS on the right surrounding the lenticulostriate artery, seen reaching just short of the caudate. C. 3D Saggital FIESTA-C image shows corrugated tube appearance of ePVS.*

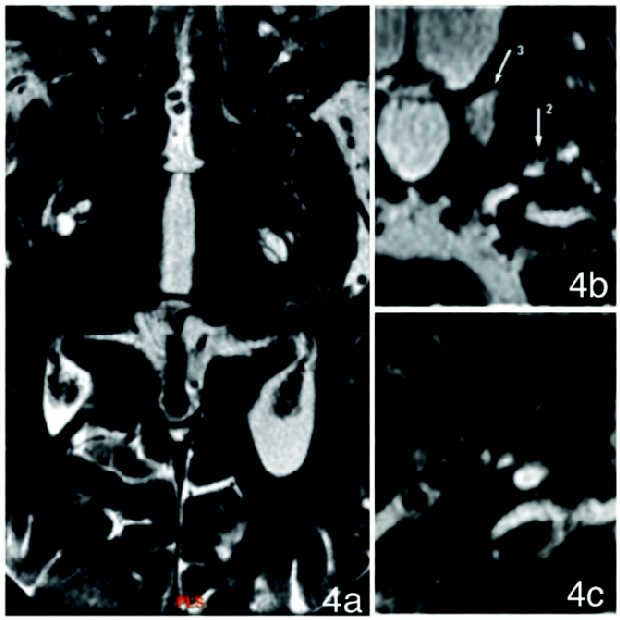

Fig. 4: *65-year-old male hypertensive, A. 3D Axial FIESTA-C image shows Irregular ePVS seen in bilateral infraputaminal section B. typical pencil tip end seen on left side. Image shows tubular CSF intensity C. 3D coronal FIESTA-C image shows wedge shaped Lacunar infarct in left thalamus, separate from the PVS.*

Comparison of WMH and ePVS in study subjects

ePVS was seen in 56 (91.8%) cases and 13 (22.03%) controls ($p < .0001$, Chi square test).

Grade 0 ePVS was seen in three (4.92%) cases and 44 (74.58%) controls ($p < .0001$, Chi square test).

In all age groups among hypertensives, the number of cases with ePVS were significantly more than number of cases showing WMH ($p < .0001$, Fisher's Exact test).

Results of data analysis

Table 2:- Sensitivity, specificity, positive predictive value and negative predictive value of PVS and WMH for predicting lacunar infarct in total study subjects.

Lacunar infarct	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
PVS	100% (84.56% to 100.00%)	52.04% (41.71% 62.24%)	0.76 (0.67 to to 0.83)	31.88% (21.17% to 44.21%)	100% (93.02% to 100.00%
White matter hyperintensity	31.82% (13.86% to 54.87%)	87.76% (79.59% to 93.51%)	0.6 (0.50 to 0.69)	36.84% (16.29% to 61.64%)	85.15% (76.69% to 91.44%)
p value	**0.016**	**< 0.0001**	–	–	–

There was 100% sensitivity of PVS in predicting lacunar infarct in hypertensives across all age groups, with maximum diagnostic accuracy seen in the 41 to 50 years age group (Table III).

Table III: Sensitivity, specificity, positive predictive value and negative predictive value of PVS and WMH for predicting lacunar infarct in hypertensive in age group 41 - 50 years.

Lacunar infarct	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
PVS	100% (15.81% to 100.00%)	26.32% (9.15% to 51.20%)	0.63 (0.40 to 0.83)	12.5% (1.55% to 38.35%)	100% (47.82% to 100.00%)
White matter hyper intensity	0% (0.00% to 84.19%)	100% (82.35% to 100.00%)	0.5 (0.28 to 0.72)	–	90.48% (69.62% to 98.83%)
p value	–	**0.0001**	–	–	–

In the 51 to 60 years age group, the diagnostic accuracy (AUC .50, PPV 40%) of WMH to predict lacunar infarct was marginally better than that of ePVS (AUC .52, PPV 50 %).

In the 61 to 70 years age group diagnostic accuracy of WMH (AUC .44, PPV 54.55%) was less than that of PVS (AUC .05, PPV 60%). ePVS showed highest odds ratio among all the predictors of lacunar infarct (Table IV).

Table IV: Univariate logistic regression to find out predictors of lacunar infarct.

Variable	Beta co-efficient	Standard error	p value	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound (95%)
Age (years)	0.118	0.038	**0.002**	1.126	1.045	1.213
Gender						
Female				1.000		
Male	0.104	0.675	0.878	1.109	0.295	4.166
PVS	1.970	1.641	0.230	7.174	0.288	178.900
White matter hyperintensity	0.914	0.637	0.151	2.494	0.716	8.689
Smokers	0.119	0.780	0.879	1.126	0.244	5.189
Diabetes	0.627	0.864	0.468	1.872	0.344	10.182
Dyslipidaemia	0.348	0.813	0.669	1.416	0.288	6.971

Discussion

The vascular 'Centrencephalon', the phylogenetically primitive part in the basal region of the brain is perfused by short straight arteries that transmit high pressure over a short distance directly from the large arteries to end arterioles. The present study centres around this region where true lacunar infarcts occur due to hypertension induced small vessel disease[16]. Study participants with large artery atherosclerosis and cardiac conditions that were likely sources of embolism were excluded from the study. Study subjects with focal pathology in the parent MCA that can obstruct the orifices of the perforating arteries and those with macro/micro haemorrhages, more likely caused due to amyloidopathy were also left out from the study to include cases with true lacunar infarcts caused by hypertension induced small vessel disease[12]. The strict eligibility criteria for inclusion was a major strength of this study.

Lacunar infarct was present only in cases and absent in controls which confirmed the strong association of lacunar infarct with hypertension. Lacunar infarct being a prototypical and quantifiable imaging feature determined the presence of cSVD in our study[8]. This was another strong point of our study as most other studies have considered the highly subjective clinical manifestation of cognitive impairment for presence of cSVD[7,17,18]. Only Deep WMH present in the centrum semiovale, fed by arterioles prone to arteriosclerosis was included in the scoring of WMH, as the Juxta cortical white matter having a dual blood supply is unlikely to be susceptible to cSVD[13].

Late emergence and progression of WMH grade was noted in the 50 to 70 years age bracket. WMH was not seen exclusively in hypertensives. Other studies have also shown WMH to be multifactorial in aging individuals[17].

Lateral striate arteries are very thin calibre arteries, that arise from the horizontal segment of the MCA and enter the substantia innominata through the anterior perforated substance[16]. These then ascend and turn medially across

the putamen and internal capsule to reach the border zone of corona radiata via the caudate. Visualisation of PVS was clearly improved by use of FIESTA C, which remained a major strength of our study. Used in the 3D mode, it provided high spatial resolution and high signal from the PVS which were seen as CSF intensity tubular structures that followed the orientation of the lateral striate arteries on coronal and saggital images and could easily be distinguished from lacunes. Striate arteries seen within few of the perivascular spaces further helped in differentiating the larger spaces from lacunes.

The results of this study supported the notion that ePVS in basal ganglia are an early and independent MRI marker of cSVD. ePVS was seen in 56 (91.8%) cases and 13 (22.03%) controls ($p < .0001$, Chi square test). A strong association of ePVS with hypertensives was seen in our study ($p < .0001$).

Across all age groups, the number of cases with ePVS were significantly more than number of cases showing WMH ($p < .0001$, Fisher's Exact test). This difference was more significant in the 41 to 50 years age group. In the 60 to 70 years age group, the difference somewhat balanced out and became minimal. Hurford *et al* found a strong relationship between basal ganglia PVS severity and hypertensive arteriopathy of cSVD[18].

The abrupt change in caliber from large arteries and perpendicular orientation of perforating arteries renders them susceptible to the pulse pressure. A double meningeal wrapping of striate arteries compared to single coat in most other cerebral vessels which further affects their drainage with early visualisation of PVS in this region[19]. In our study, PVS were most prominent in the substantia innominata. The perforating end arteries in this region are susceptible even to the high impact of normal blood pressure as seen by presence of grade 0 (less than five) ePVS in significant number of controls.

Our study results showed that diagnostic accuracy of PVS in predicting lacunar infarct was significantly higher than that of WMH in overall study subjects confirming ePVS as a useful imaging marker of cSVD.

Hansen *et al*[17] also found PVS dilation to be a useful biomarker of SVD. PVS appeared more specific and retained greater discriminative power than WMH to distinguish patients with vascular dementia from healthy individuals.

In the Northern Manhattan study[20], stroke free participants were followed-up for an average of 9 ± 2 years. Those with higher ePVS scores on initial MRI had higher incidence of vascular complications especially if their pulse pressure or systolic blood pressure was elevated. Study performed by Loos *et al*[21] showed extensive Basal Ganglia PVS on MRI in 118 patients with lacunar stroke was associated with progression of WMH on follow-up MRI after two years. However, presence of WMH at baseline remained an important determinant of further progression of WMH in cSVD.

Yang *et al*[22] found 24 hour BP variability to be associated with lacunar infarctions and WMH. Ambulatory BP was also independently associated with the degree of ePVS in basal ganglia. In a study by Klarenbeek *et al*[23], higher day time ambulatory BP level was found to be associated with enlarged PVS in the basal ganglia. This association was independent of the presence of WMH and lacunar infarcts.

Our cases comprised of patients with history of long standing hypertension or hypertensives with non compliance to drug therapy. We did not correlate ePVS with the ambulatory BP of our study subjects as in studies by Yang *et al*[22] and Klarenbeek *et al*[23]. This was another limitation of our study.

We selected non-hypertensive patients in the same age range as the cases to form a non-hypertensive control group for comparative analysis which added statistical power to our study.

Age, gender, diabetes, dyslipidaemia and smoking which could be confounding variables were taken care of both in the design stage by matching and univariate logistic regression in the analysis stage of the study. A high odds ratio showed strong association between PVS and lacunar infarct in hypertensives in the present study without a wait for a long latency period needed in cohort studies[20,21]. However, true causal relationship between ePVS and and cSVD could not be established as in the follow-up studies which could be another limitation of our study.

Conclusion

Peri-vascular spaces in the brain should not simply be overlooked as an inevitable consequence of aging. Visual estimation of the number and distribution of PVS on MRI has the potential to be an early and independent imaging marker of Cerebral Small Vessel Disease, a prevalent but often unrecognised disorder. ePVS in basal ganglia could be utilised in clinical practise to slow down and if possible halt the progression of hypertension induced cSVD before it reaches the stage of cognitive decline.

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