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Cognitive Dysfunction in Relation to Topography and Burden of Cerebral Microbleeds

Serebral Mikrokanama Yükü ve Yerleşiminin Kognitif Disfonksiyon ile İlişkisi

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ABSTRACT

Introduction: Contribution of cerebral microbleeds (CMBs) on cognitive dysfunctions in elderly patients with otherwise asymptomatic white matter lesions (WMLs) is not well-documented.

Methods: MRI parameters of cerebral atrophy, CMBs and WMLs were herein analyzed in relation to global and main domains (attention, executive, memory, visuospatial, language) of cognitive function. Eighty-five patients older than 50, without neurodegenerative/cerebrovascular disease, but had CMBs were recruited from 2562 with T2*-gradient-echo MR imaging during one-year period.

Results: Global cognition, evaluated by mini-mental status examination (MMSE), was impaired (score ≤24) in 42%. In contrast to CMBs load, WML burden and temporal atrophy were significantly higher in cases with MMSE≤24. Cholinergic Pathways HyperIntensities Scale (CHIPS) was positively correlated with global cognitive dysfunction but its CMB counterpart, Cholinergic Pathways Bleeding Scale described herein, was not. However, burden of CMBs in thalamic/cortical regions predicted language dysfunction.

Conclusion: Cognitive dysfunction associated with CMBs may be dependent on their distribution rather than their absolute number.

Keywords: Cholinergic, dementia, microbleed, lacune, white matter, cortex, cortical, magnetic resonance imaging, gradient echo

ÖZ

Amaç: Manyetik rezonans (MR) görüntülemede diğer açılardan asemptomatik serebral beyaz cevher lezyonu (SBL) saptanan yaşlılarda bulunan serebral mikrokanamaların (SMK) kognitif fonksiyonlara olan etkisi yeterince ayrılıp dokümante edilmiş değildir.

Yöntem: Serebral atrofi, SMK ve SBL'nin MR parametreleri ile kognisyonun global ve ana eksenleri (dikkat, yürütücü, hafıza, görsel-uzaysal ve lisan) arasındaki bağlantı tesadüfen SMK saptanan yaşı elliden büyük 85 hastada çalışıldı. Tanı almış nörodejeneratif ve nörovasküler hastalığı olmayan bu çalışma popülasyonu, bir yıl süresince T2*-gradient eko sekansı ile beyin MR çekilmiş olan 2562 olgu arasından geriye dönük olarak tespit edilip muayeneye çağrıldı.

Bulgular: Global kognisyon, olguların %42'sinde mini-mental durum muayenesine göre (MMSE, ≤24 ise bozuk kabul edilir) anormaldir. SMK yükü değil ama SBL yoğunluğu ve temporal atrofi MMSE≤24 olanlarda daha yüksek orandadır. "Kolinerjik Yolakların Hiperintensiteleri Skalası" (CHIPS) global kognitif disfonksiyon ile korele iken, bunun SMK eşleniği (bu çalışmada tanımlanan "Kolinerjik Yolakların Mikrokanama Skoru") değildir. Ancak, özellikle talamik ve kortikal SMK yükünün subklinik lisan disfonksiyonu ile bağlantısı dikkati çekmiştir.

Sonuç: SMK ile bağlantılı kognitif disfonksiyonun mutlak adet ile değil lokalizasyon ve dağılımla daha çok ilgili olduğunu işaret etmektedir.

Anahtar kelimeler: Kolinerjik, bunama, mikrokanama, lakün, beyaz cevher, korteks, kortikal, manyetik rezonans görüntüleme, gradient eko

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INTRODUCTION

Cerebral microbleeds (CMBs) represent perivascular collections of hemosiderin deposits, and they appear as dot-like hypointense lesions on T2*-weighted gradient-recalled echo (GRE) and susceptibility-weighted magnetic resonance imaging (MRI) (1). In parallel to expanded usage of these iron sensitive MRI techniques in clinical and research arena, the need for understanding clinical implication of CMBs has become an active area of research. Pathologically, CMBs are linked to cerebral amyloid angiopathy and/or hypertensive vasculopathy; and recognized as MRI indices of small vessel disease along with white matter hyperintensities and lacunes (2–4). CMBs are not uncommon in healthy adults with a prevalence of around 5% (5). An increased prevalence has been reported in normal ageing, and individuals with cerebrovascular

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disorders and dementia (3, 4). In stroke patients, the presence, distribution and burden of CMBs are increasingly being recognized as valuable marker of etiology, stratification of future vascular risk including mortality along with modification, and monitoring of treatment (6). There has been also growing evidence for cumulative and/or strategic effect of otherwise silent CMBs on chronic neurological disability such as gait dysfunction (7), or cognitive decline (4, 8). However, these evidences are not as consistent as WMLs (9). Observational cross-sectional nature of the published studies (10–18); inclusion of the subjects with various neurological illnesses already associated with cognitive decline, e.g. Alzheimer's disease (11, 16, 19, 20), subcortical vascular dementia (14), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (17, 21, 22), and stroke (23), as well as insufficient adjustment for other neuroimaging markers of small-vessel disease including white matter lesions (WML), or lacunar infarctions (11, 13); and absence of detailed cognitive profiling may be among the reasons for observed heterogeneity of these studies. Moreover, site of sampling of subjects –e.g. memory/cognitive neurology clinics (12, 13, 24), neurovascular units (15, 23)– may also be a factor. In population based cross sectional studies that compared the cognitive profiles of neurological disease-free subjects with and without CMBs, CMBs burden of subjects are usually low (15, 18, 25–27). On the other hand, in subjects recruited from memory clinics or neurovascular units CMB burden is usually higher. As a result, while no association of CMBs and cognitive dysfunction was observed in some studies (11, 13, 16), others documented a connection with either global (17, 18, 26) or domain-specific (12, 14, 15, 24–27) cognitive decline. Executive dysfunction was a frequent finding in subjects with CMBs (12, 26, 27), and it was related to frontal and temporal lobar predilection of CMBs (26).

In this study, we assess the relationship between CMBs/WML and cognitive function in patients with apparently-asymptomatic small vessel disease. Our specific interest is the definition of the effect of topographic distribution of CMBs, particularly involvement of cholinergic pathways, on cognition in addition to their number.

METHODS

Subjects

A total of 2562 subjects older than 50 years of age who underwent GRE imaging as part of brain MRI study at Hacettepe University Department of Radiology during a one-year-period (from December 1, 2009 to November 31, 2010) were screened for the presence of CMBs. In our institution, T2* GRE sequences are routinely obtained in diagnostic MRI studies for patients older than 50 years. We observed at least one CMB in 300 (11.7%) subjects. patients with a known diagnosis of neurodegenerative diseases or symptomatic cerebrovascular disorders (n=209) were excluded to restrict the study population to subjects with asymptomatic small vessel disease. The remaining 91 subjects were contacted via telephone, and were invited for neuropsychological assessment. Six patients died during the interval between the MRI study and our phone call. The remaining 85 subjects comprised the study population. Informed consent was obtained from all subjects. Hacettepe University Ethical Committee approved the study protocol. As a global measure of cognition, Mini-Mental State Examination (MMSE) was applied to all patients, and those with MMSE score below 24 are classified as cognitively impaired. Linear measures of cerebral atrophy, the number and topography of CMBs, WMLs and lacunes were comparatively analyzed in patients with and without cognitive impairment.

Cognitive Profiling

A neuropsychological test battery measuring attention (digit span forward, trail making (TMT) A test), executive functions (TMT B, five-point test, and phonemic fluency tests), memory (Rey's auditory verbal learning test (AVLT), enhanced cued recall (ECR), category (semantic) fluency, visual reproduction subtest of Wecshler's memory scale (immediate memory: WMS-VRI and delayed memory: VRII), visuospatial abilities (clock drawing test, line orientation test and Benton's face recognition tests (FRT), language (30-item versions of the Boston naming test (BNT), phonemic fluency), and geriatric depression scale was administered. Scoring and administration of these tests have been described previously (28–37).

Neuroimaging Studies

MRI Parameters

MRI was performed using a 1.5-T scanner (Magnetom TIM, Siemens, Erlangen, Germany). Imaging included sagittal and axial T1-weighted (W) (time of repetition (TR)/time of echo (TE); 515/15 ms, matrix (mtx): 192 x 256) spin echo (SE), coronal and axial T2-W turbo SE (TR/TE; 4000/100 ms, mtx: 256 x 448), axial fluid-attenuated inversion-recovery (FLAIR) (TR/TE/TI; 8100/100/2100 ms, mtx: 224 x 256), and T2* gradient-echo (TR/TE; 860/26 ms, flip angle: 20°, mtx: 192 x 256) sequences all with a slice thickness of 5 mm, a 10% inter-slice distance and 220–240 mm field of view (FOV).

Lesion Interpretation and Analyses

Linear measures of atrophy, ratings of WMLs and CMBs were assessed blindly and independently by a study neurologist [MAT], and a study neuroradiologist [RG]. In case of discrepancy, scans were re-evaluated by the senior neuroradiologist [KKO] and another study neurologist [EMA]; and consensus scores were used in multivariate analyses.

White matter lesions: WMLs were evaluated on FLAIR and T2-weighted images. Three semi-quantitative rating scales were used to analyze the extent and location of WMLs: Fazekas' scale (38), Shelten's or Age-Related White Matter Changes (ARWMC) scale (39), and Cholinergic Pathways HyperIntensities Scale (CHIPS) (40). The intra-class correlation coefficients were excellent for Fazekas' subcortical and periventricular scores (0.971 and 0.952, respectively), and for ARWMC scale (0.963). The intra-class correlation coefficient for CHIPS scale was good (0.897).

FLAIR images were also used for analysis of lacunes. They were defined as small (3 mm < diameter < 15 mm) hypointense lesions with a peripheral hyperintense rim located within the territory of a single perforating artery. Lacunes located within the cerebellum were excluded from the analyses. The intra-class correlation coefficient for lacune number was moderate (0.704 if total number <5; 0.697 if total number ≥5).

Cerebral microbleeds: CMBs were evaluated on GRE MRI. Round signal void areas with a diameter smaller than 10 mm were assigned as CMBs in concordance with the recent guide on detection and interpretation by the Microbleed Study Group (1). The intra-class correlation coefficient for CMB number was good (r=0.968 in all; r=0.699 if CMB number ≤5; r=0.950 if CMB number between 6 and 19; r=0.710 if total number ≥20).

The topographic distribution of CMBs was determined according to the areas included in both BOMBS (Brain Observer MicroBleed Scale) (41), and MARS (The Microbleed Anatomical Rating Scale) (42). Accordingly, CMB location was recorded as lobar (frontal, temporal, parietal, insular and occipital), deep (basal ganglia, external capsule, internal capsule, thalamus, corpus callosum, and deep and periventricular white matter), and infratentorial (medulla oblongata, cerebellum, pons, and mesencephalon) separately on both sides of the brain. Additionally, Cholinergic Pathways Bleeding (Microhemorrhage) Scale (CHBS), which is analogous to CHIPS (40), was described and used to evaluate the effects of CMBs on cholinergic pathways. The intra-class correlation coefficient for CHBS was good (r=0.810).

Linear measures of atrophy: Inter-uncal distance (IUD: linear distance between the unci of temporal lobes), bitemporal distance (BTD: distance

between outer margins of temporal lobes), and intracranial temporal width (ICTW: distance between the inner cranium) were measured at the level of suprasellar cistern on T1-weighted images (36, 43). IUD was normalized against ICTW (normalized (n) IUD = IUD/ICTW * 100) to exclude the effect of individual head size. We further calculated uncotemporal index (UTI = IUD/BTD * 100) (43). Intercaudate distance (ICD: linear distance between the medial borders of caudate nuclei) and intracranial caudate level width (ICCW: distance between table of the skull) were measured on the caudal-most axial slice where caudate nuclei and lateral ventricles could be visualized independent of image acquisition technique or slice thickness again on T1-weighted images. Further, intercaudate ratio (ICR: ICD/ICCW * 100) was provided to normalize ICD values (44). Intra-class correlation coefficients for all of the atrophy indices ranged from good to excellent: r=0.820 for IUD; r=0.763 for BTD; r=0.803 for ICTW; r=0.722 for nIUD; r=0.751 for UTI; r=0.882 for ICD; r=0.825 for ICCW and r=0.851 for nICD. Four cases with *cavum septi pellucidi et vargae* were excluded from caudate level measurements.

Statistical Analysis

Comparison of demographic features, MRI findings (WML scores, CMBs, lacune numbers, linear measures of atrophy), and neuropsychological test scores between cognitively impaired and cognitively unimpaired groups were carried out by Student's t-test, Mann-Whitney's U test, and chi-square as appropriate. The effect of MRI on cognition was first evaluated with correlation analysis. Then, using MRI variables with p<0.10 in univariate analysis, in addition to age and school years, were entered into logistic regression analysis in order to determine the significance and independent role played by these factors in subjects' performance on neuropsychological tests, which were further categorized into several aforementioned domains as attention, executive, memory, visuo-spatial, and language, in addition to global view assessed with total MMSE score. Statistical analyses were performed using the SPSS® (Statistical Package for the Social Sciences, version 21). All values were displayed as "mean ± standard deviation of the mean", "median" or "percentage" where applicable. A gray-scale coding of p-values of correlation and regression analyses was displayed in Figure 1A and 1B for summary. Statistical significance level was set at p<0.05 in all analyses despite the presence of multiple comparisons due to the exploratory nature of the study.

RESULTS

Global cognition, evaluated by MMSE, was normal in 58% of subjects; and impaired in 42%. Demographics and results of neuropsychological tests are summarized in Table 1. Compared to subjects with normal global cognition, those with impaired cognition had significantly higher WML burden and more significant temporal atrophy. However, these two groups were not statistically different in terms of CMB number and location (Table 2).

We next sought relation of imaging findings with various cognitive functions in the whole study population. First of all, MMSE scores showed significant and inverse correlation with white matter disease measures and linear temporal volume measures but not with CMB number and distribution (Figure 1A). The most significant correlation was with the CHIPS (r=-0.484). Regression analysis revealed CHIPS (p=0.01) and nIUD (p=0.029) along with education year (p=0.001) as significant independent predictors of MMSE (Figure 1B). Of note, the relationship between MMSE, and left hemispheric cortical CMB burden and UTI reached borderline significance in this model.

Table 1. Demographic characteristics and cognitive profile

		Impaired general cognition (n=36)	Normal general cognition (n=49)	p
Age		72±8	69±8	0.050
Female gender		50%	33%	0.122
Education years		4±4	7±5	0.003
Hypertension		92%	92%	0.978
Diabetes Mellitus		14%	18%	0.582
Coronary Artery Disease		17%	25%	0.383
Hyperlipidemia		28%	39%	0.291
Average MMSE		20±3	27±3	<0.001
Geriatric depression scale		8±3	8±5	0.959
Attention	Digit span forward	4.4±0.9	5.3±1	<0.001
	Trial making test A	138±64	83±34	0.002
Executive function	Trial making test B	292±26	218±79	<0.001
	Five point test	11±6	22±8	<0.001
	Phonemic fluency	12±3	16±4	<0.001
Memory	AVLT	5.2±2.4	8.7±3.3	<0.001
	Enhanced Cued Recall	37±7	45±5	<0.001
	Category fluency	12±3	16±4	<0.001
	WMS, VR I	3.6±3.3	7.6±3.9	<0.001
	WMS, VR II	2.7±3.1	6.1±3.7	<0.001
Visuo-spatial abilities	Clock drawing test	1.5±1.5	2.9±1.7	<0.001
	Line orientation test	11±3	16±5	<0.001
	Face recognition test	32±6	37±4	0.001
Language	Boston naming test	23±4	27±3	<0.001

MMSE, Mini-Mental State Examination; AVLT, Rey's auditory verbal learning test; WMS-VR I & II: Visual reproduction subtest of Wecshler's memory scale (immediate memory: WMS-VRI and delayed memory: VRII).

Table 2. MRI Findings

		Impaired general cognition (n=36)	Normal general cognition, (n=49)	p
Fazekas' subcortical score	0	3%	10%	0.005
	1	22%	51%	
	2	42%	29%	
	3	33%	10%	
Fazekas' periventricular score	0	6%	18%	0.071
	1	19%	31%	
	2	39%	35%	
	3	36%	16%	
ARWMC		13±6	9±7	0.004
CHIPS		30±27	10±15	<0.001
Number of lacunes		4±4	2.6±4	0.081
Number of CMBs		21±30	16±32	0.479
Supratentorial CMB number		19±30	13±26	0.289
Lobar CMB number		14±29	9±25	0.415
Cortical CMB number		11±28	5±9	0.171
Thalamic CMB number		3±5	2±4	0.217
CHBS		1.8±3.1	1.3±3.8	0.573
Inter-uncal distance (cm)		2.9±0.4	2.7±0.4	0.038
Bitemporal distance (cm)		12.6±0.6	12.8±0.8	0.200
Normalized Inter-uncal distance (%)		22±3	20±3	0.002
Uncotemporal index (%)		23±3	22±3	0.006
Intercaudate distance (cm)		2.0±0.5	1.9±0.5	0.354
Normalized Intercaudate distance (%)		16±4	15±3	0.261

ARWMC, Shelten's or Age-Related White Matter Changes scale; CHIPS, Cholinergic Pathways HyperIntensities Scale; CMB, Cerebral microbleed; CHBS, Cholinergic Pathways Bleeding (Microhemorrhage) Scale

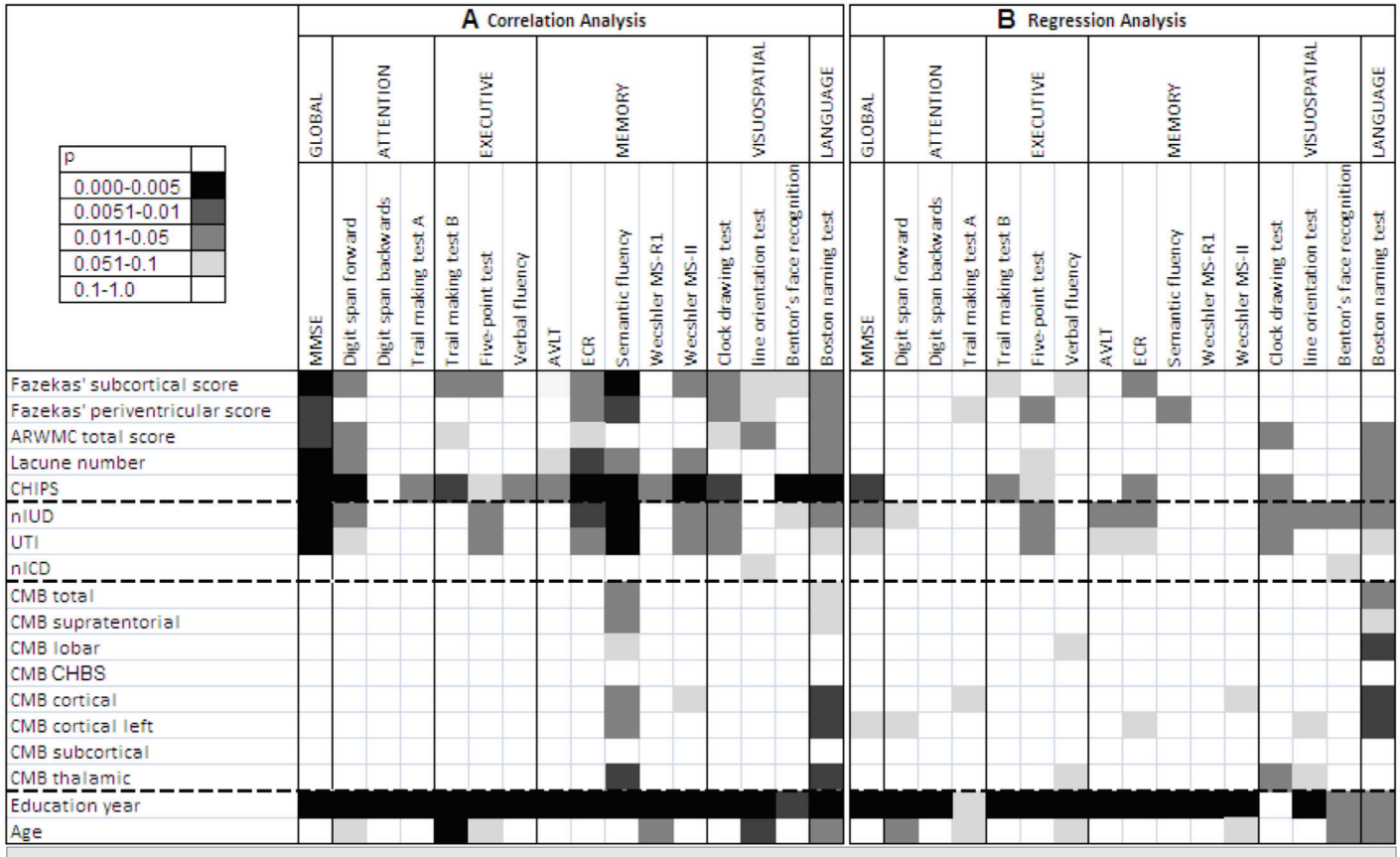

Figure 1. A, B. Summary of relationship between MRI parameters and cognitive domains.

MMSE, Mini-Mental State Examination; AVLT, Rey's auditory verbal learning test; ECR, enhanced cued recall test; Wecshler MS-R1, Visual reproduction subtest of Wecshler's memory scale (immediate memory); Wecshler MS R2, Visual reproduction subtest of Wecshler's memory scale (delayed memory); ARWMC, Shelten's or Age-Related White Matter Changes scale; CHIPS, Cholinergic Pathways HyperIntensities Scale; nIUD, normalized Inter-uncal distance; UTI, uncotemporal index; nICD: normalized Intercaudate distance; CMB, Cerebral microbleed; CHBS, Cholinergic Pathways Bleeding (Microhemorrhage) Scale.

Attention was assessed by digits span forward and TMT-A tests. Digit span forward scores showed marginal but significant correlation with the CHIPS (r=-0.322, p=0.003), ARWMC (r=-0.252, p=0.022), lacune number (r=-0.237, p=0.032), Fazekas' subcortical score (r=-0.261, p=0.016) and nIUD (r=-0.231, p=0.038). CHIPS were also correlated with TMT-A scores (r=-. 291, p=0.027). However, none of these imaging features showed a significant association with measures of attention in regression analyses (Figure 1A and B).

Executive function was evaluated with three tests. A significant correlation was found between TMT B scores and Fazekas' subcortical score (r=0.295; p=0.029) as well as CHIPS (r=0.346; p=0.01). CHIPS was also significantly correlated with the phonemic fluency (r=-0.242, p=0.033), but not with 5-point test (r=-0.189; p=0.083). Furthermore, regression analysis showed a modest but significant effect of CHIPS on executive function when tested by TMT-B (p=0.045). Fazekas' periventricular score (p=0.046), together with nIUD (p=0.016) and UTI (p=0.042) were significantly associated with the results of 5-point test in regression analysis.

Memory function was assessed by 5 neuropsychological tests. There were significant correlations between CHIPS and all of the tests: r=-0.265, p=0.018 for AVLT, r=-0.320, p=0.004 for ECR; r=-0.346, p=0.001 for semantic fluency; r=-0.274, p=0.021 for WMS-VRI and r=-0.298, p=0.006 for WMS-VRII. AVLT was not significantly correlated with other WML scores albeit a tendency was notable for lacune number (r=-0.211, p=0.06). ECR scores were correlated with Fazekas' subcortical and periventricular scales (r=-0.221, p=0.047 and r=-0.274, p=0.013, respectively), and lacune number (r=-0.305, p=0.006). A significant correlation existed between ECR and atrophy indices (nIUD: r=-0.289, p=0.009 and UTI: r=-0.227, p=0.043). WML (r=-0.357, p=0.001 for Fazekas' subcortical score; r=-0.292, p=0.007 for Fazekas' periventricular score; r=-0.220, p=0.043 for lacune number) and atrophy indices (r=-0.372, p=0.001 for nIUD; r=-0.336, p=0.002 for UTI) were also correlated with semantic fluency. Semantic fluency was the only test showing a correlation with CMB number in various locations (r=-0.245, p=0.024 for total CMBs; r=-0.246, p=0.023 for supratentorial CMBs; r=-0.202, p=0.064 for lobar CMBs; r=-0.230, p=0.037 for cortical CMBs; r=-0.290, p=0.007 for thalamic CMBs). While WMS-VRI did not show any correlation with MRI parameters except for CHIPS score, WMS-VRII was correlated with both atrophy indices (r=-0.258, p=0.018 for nIUD and r=-0.251, p=0.021 for UTI) and several WML parameters (r=-0.250, p=0.021 for Fazekas' subcortical score; r=-0.219, p=0.045 for lacune number). Regression analysis showed nIUD as an independent predictor of AVLT and ECR abnormalities (p=0.044 and p=0.031, respectively) in addition to education years. In addition to nIUD, Fazekas' subcortical score (p=0.013) and CHIPS (p=0.044) were significantly associated with ECR. Fazekas' periventricular score was significantly associated with poor performance on semantic fluency test in multivariate analysis (p=0.028). Of note, no significant association between CMBs and memory function was observed in regression analyses although a trend for association was noted between ECR and left cortical CMB number (p=0.060), and between WMS-VRII and cortical CMB number (p=0.053).

Visuospatial abilities were studied with 3 tests. A significant correlation was noted between clock drawing test and Fazekas' subcortical score (r=-0.227, p=0.037), Fazekas' periventricular score (r=-0.228, p=0.028), CHIPS (r=-0.285, p=0.008), nIUD (r=-0.261, p=0.017) and UTI (r=-0.240, p=0.028). ARWMC was the only imaging measure significantly correlated with line orientation test (r=-0.345, p=0.019), while CHIPS was the only measure significantly associated with Benton face recognition tests (r=-0.304, p=0.005). Correlation analyses did not show any significant relationship between CMB parameters and visuospatial tests. Regression analysis documented that nIUD was an independent predictor for abnormal clock drawing (p=0.029), line orientation (p=0.024), and Benton's face recognition tests (p=0.020). UTI (p=0.040), CHIPS (p=0.025), ARWMC (p=0.038), and thalamic CMB number (p=0.006) were the other independent variables that showed a significant association with abnormal clock drawing test results.

Language was assessed with 30-item versions of the Boston naming test. BNT showed weak but significant correlation with WML (Fazekas' subcortical score: r=-0.258, p=0.017; Fazekas' periventricular score: r=-0.245, p=0.024; ARWMC: r=-0.226, p=0.037; CHIPS: r=-0.316; p=0.003; lacune number. r=-0.252, p=0.020), and atrophy indices (nIUD: r=-0.253, p=0.020; UTI: r=-0.201, p=0.066). Furthermore, BNT scores were correlated with thalamic (r=-0.301, p=0.005) and cortical CMBs (r=-0.285, p=0.009), especially with the ones located in the left-hemisphere (r=-0.291, p=0.007). Regression analysis showed nIUD (p=0.011), CHIPS (p=0.044), ARWMC (p=0.022), lacune number (p=0.050), together with CMB burden (p=0.003 for cortical, p=0.001 for left-sided cortical, p=0.002 for lobar, and p=0.037 for total CMB number) as independent predictors of abnormal BNT performance.

DISCUSSION

This study showed that in an older adult population recruited from imaging center regardless of primary illness or complaint leading to hospital admission and MR acquisition but had imaging evidence of small vessel disease, MR measures of white matter hyperintensity and cortical atrophy are more prominent in patients with objective measures of cognitive impairment. In contrary, number and location of CMB did not differ between cognitively impaired and unimpaired subjects. General cognition and individual cognitive domains including attention, executive function, memory, and visuo-spatial abilities were related to WML burden, involvement of cholinergic tracts by WMLs, and temporal lobe atrophy. This relation showed that cognitive functions are poorer in patients with higher WML burden and cortical atrophy. On the other hand, there was no association between CMB burden and global cognitive ability assessed by MMSE. We also could not find any significant association between MMSE and spatial distribution of CMBs, which was not only analyzed according to anatomic localization (such as thalamic, cortical or lobar, and right or left), but also at the network-level via CHBS, which quantifies subcortical cholinergic network involvement. Our analyses took into account potential confounders that might affect global cognitive ability including age and education level along with detailed MRI measures such as cerebral atrophy, number of lacunes, and WML burden. Similarly, no significant relationship between CMB burden and topography was observed with performances of subjects in tests assessing attention, executive function, and memory, while there was a significant association in scores of BNT, a language test which measures confrontational word retrieval, and scores of clock drawing test which measures both construction and planning abilities of visuo-spatial function and language.

A large number of studies demonstrated that WMLs are associated with mild cognitive impairment and dementia (45, 46). Some of those and other studies also showed that higher WML burden is related to cognitive decline or worse cognitive status in elderly patients regardless of diagnosis (45–47). Volumetric studies and also less sophisticated linear cerebral atrophy measures consistently revealed that cerebral and most specifically hippocampal atrophy is an independent predictor of cognitive decline in neurodegenerative diseases (36, 45). Our findings are in agreement with these studies, and further confirm it in an older adult population with asymptomatic small vessel disease.

The relation of CMBs on cognitive impairment is more inconsistent in the literature. Some studies reported a connection with global cognitive decline (17, 18, 26) or domain-specific cognitive functions such as executive function (12, 14, 15, 24–27); but the others reported lack of association of CMBs and cognitive dysfunction (11, 13, 16). A novel finding

of the present study was a significant and independent association between number of cortical CMBs on the left hemisphere and BNT performance. In addition, thalamic CMB burden was related to lower semantic fluency scores in correlation analysis, but this relationship did not persist on regression analysis. On the other hand, we could not find a similar relation with phonemic fluency ability, another language related test, albeit a trend was notable for lobar and thalamic CMB burden. This discrepancy may be explained by a regional difference where those functions depend on. Semantic fluency and BNT assess semantic processing and word production, and are considered as a function of the dominant temporal lobe, while phonemic fluency is considered as a function of the frontal lobe of the dominant hemisphere (48). Considering a temporo-occipital dominant distribution of CMBs, it is plausible to expect impairment in the former 2 tests in patients with high CMB burden.

We also found a weak but significant relation between CMB burden in thalamus and clock drawing test performance. Clock drawing test is traditionally considered as a measure of visuo-spatial function, and is used to test parietal lobe function. However, other elements of mental function including planning, mental rotation, understanding, and carrying out numeric and linguistic information are required during this task. Therefore, success in this test is dependent on an intact network that spans more than one anatomic location. Indeed, previous studies have pointed out a relationship between right parietal, left frontal and basal ganglia lesions, and impairment in this test (49). Further studies are necessary to confirm a potential role of thalamus in clock drawing test, as suggested by our findings.

The major strength of our study is the prospective and consecutive enrollment of all eligible subjects from an imaging center of a university hospital that serves patients with diverse medical illnesses, preventing the sampling bias. On the other hand, the limitation of our study is the absence of a control group that does not have CBMs. With these reservations in hand, our study showed that the relationship between CMB and cognition is topography dependent. In other words, according to our observation, cognitive effect of CMBs seems to be related to their strategic location rather than their absolute number. This observation might also explain the heterogeneity in reports focusing on the relationship between CMBs and cognition to some extent. It is clear that further studies are required to clarify the potential relevance of CMBs in cognitive function of otherwise neurologically healthy individuals. In addition, longitudinal population based studies exploring effect of CMBs on cognitive change over time would also help us understand whether CMBs have additive or synergistic effect in lowering the threshold for dementia in subjects with vascular and degenerative disorders.

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