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ORIGINAL COMMUNICATION

Cerebral microbleeds are associated with cognitive decline early after ischemic stroke

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Abstract

Background and purpose The present study aimed to investigate whether cerebral microbleeds (CMB) are associated with vascular cognitive decline (VCD) already in the early course after ischemic stroke, and—if so—whether distinct cognitive domains are affected more preferentially by CMB.

Methods In a prospective cohort study, cognitive performance was examined in 33 stroke patients showing ≥1 CMB on MRI. Matched for age, gender, clinical and radiological characteristics, 33 stroke survivors without CMB served as a control group. Neuropsychological testing was performed in both groups six months after the index event using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)-plus test battery.

Results CMB-positive stroke patients showed more severe cognitive decline in mini mental state test compared to the control group ($p=0.024$). Regarding the episodic memory, CMB-positive patients reached lower scores in Word-List-Learning- ($p=0.009$) and the Word-List-Recognition-test ($p=0.006$), whereas the findings in Word-List-Recall-test were similar in both groups. While semantic fluency is not more affected in CMB-positive than in CMB-negative patients, those with CMB reveal a significantly impaired phonemic fluency ($p=0.007$). Concerning the visuospatial abilities, stroke patients with CMB showed restricted recall of recently learned visual information. Only slight differences between both groups were found in any test investigating the participants' executive functions.

Conclusion Cognitive abilities are more severely impaired in CMB-positive stroke patients compared to CMB-free controls, whereby memory-associated functions are most affected. CMB might be associated with post-stroke cognitive decline, particularly with impaired memory and phonemic fluency.

Keywords Cerebral microbleeds · Ischemic stroke · Cognitive impairment · Magnetic resonance imaging · CERAD plus test · Executive function

Introduction

Around 50% of all stroke patients develop vascular cognitive decline (VCD) or vascular dementia according to a recent meta-anlysis [1]. White matter hyperintensities have been shown to play an important role in cognitive impairment following stroke [2, 3]. There is also growing evidence that cerebral microbleeds (CMB)—another marker for small vessel disease—are associated with cognitive dysfunction in the elderly [4–9]. However, little is known about the significance of CMB in the development of VCD after stroke [10], especially in the early course after cerebral ischemia. Additionally, most studies that examined the effect of CMB on cognitive impairment used Mini-Mental Status Examination (MMSE) and/or Montreal Cognitive Assessment (MoCA) [11]. These tests have several shortcomings such as a lack of sufficient items to measure visuospatial and/or constructive praxis appropriately [12]. Here, we aimed to investigate (1) whether CMB are associated with VCD 6 months after ischemic stroke and if so (2) whether there are some cognitive domains that are affected more preferentially by CMB evaluated by the Consortium to Establish a Registry for Alzheimer's Diseases (CERAD)-plus test battery [13].

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Methods

In a prospective cohort study, cognitive function was investigated in 33 patients with ischemic stroke or transient ischemic attack (TIA) and ≥ 1 CMB. Cognitive performance of these patients was compared with 33 stroke survivors without CMB (Stroke Unit, University Hospital of Würzburg). Both groups were matched for age, gender, clinical and radiological characteristics. CMB were defined as small circular or rounded, hypointense lesions ranging from 2 to 10 mm in size on T2*-GRE or susceptibility-weighted images (SWI)-MRI scans. The number and location of CMB were determined by consensus reading of two raters (NC, FF) on MRI performed at admission. Depending on their location, CMB were classified as 'lobar', 'cerebellar' or 'deep' (supratentorial/subcortical and brainstem). Degree of white matter lesion was assessed using the Fazekas score [14].

Six months after index event, the standardized neuropsychological test battery CERAD-plus [13] was performed to assess the cognitive function in the following domains: verbal and visual memory, naming skills, perceptual functions, frontal-executive functions (EF) as well as speed and attention. In detail, the CERAD-plus test encompasses verbal fluency (animal naming), Boston naming test (15 items), MMSE, word list learning, recall and recognition (10 words), constructional praxis and recall, furthermore trail making test A and B (TMT A and B) as well as phonemic fluency (s-words).

Comparisons of patients with versus without CMB were done for baseline characteristics (Table 1) and the aforementioned tests. CERAD-plus variables were transformed to achieve normalization of standardized residuals (z-scores) adjusting for covariates (i.e., age, education, sex). To account for α-inflation due to multiple comparisons, we adjusted the level of significance by use of Bonferroni's correction for each cognitive domain. After examining the impact of any CMB on cognitive decline (i.e., independent of the location of CMB in the brain), we investigated whether multilocular CMBs (i.e., CMBs detected in more than one of the predefined brain regions, 'lobar', 'cerebellar', 'deep') affect even more cognitive performance in the early course after ischemic stroke. Statistical analyses were performed using SPSS statistics 17.0 (SPSS, Inc., Chicago, IL, USA). The study was approved by the local ethics committee of Würzburg (AZ 223/16). All participants signed written informed consent to perform this study. Anonymous data will be shared by request.

Table 1 Participants' baseline characteristics

General characteristics	CMB+	CMB−	p-value
$N = 66$	33	33	
Age (years)			
Median	79	78	
Mean ± SD	76.6 ± 8.6	76.4 ± 10.1	0.93
Male gender % (n)	55 (18)	55 (18)	1.00
Vascular risk factors % (n)			
Hypertension	90.9 (30)	72.7 (24)	0.06
Atrial fibrillation	27.3 (9)	42.4 (14)	0.20
Smoking	12.1 (4)	12.1 (4)	1.00
Hypercholesterolemia	36.4 (12)	15.2 (5)	0.05*
Diabetes mellitus	30.3 (10)	21.2 (7)	0.41
Education (year)			
Median	11	11	
Mean ± SD	11.6 ± 2.8	11.3 ± 2.7	0.73
Index event			
Ischemic stroke % (n)	88 (29)	88 (29)	1.00
Transient ischemic attack % (n)	12 (4)	12 (4)	1.00
Clinical scores at admission			
NIHSS (mean ± SD)	3.9 ± 4.3	3.2 ± 4.6	0.50
Barthel Index (mean ± SD)	63.0 ± 28.2	66.5 ± 30.8	0.64
mRS median (25;75 percentile)	2 (1;3)	1.5 (0;2)	0.41
Fazekas score			
Mean ± SD	1.9	1.6	0.17
Distribution of CMB			
lobar % (n)			
Frontal	14 (7)		
Parietal	30 (15)		
Temporal	30 (15)		
Occipital	26 (13)		
Cerebellar (n)	14		
Deep % (n)			
Supratentorial/subcortical	88.5 (23)		
Brainstem	11.5 (3)		

CMB+ stroke survivors with cerebral microbleeds, *CMB−* stroke patients without cerebral microbleeds

Results

When assessing global cognitive function using MMSE, stroke patients with CMB showed more severe cognitive decline compared to the CMB-free group ($p = 0.024$). Next, single cognitive domains (i.e., semantic and episodic memory, constructional praxis and EF) were examined using CERAD-plus test battery. Regarding the episodic memory, CMB-positive patients reached lower scores in Word-List-Learning- ($p = 0.009$) and Word-List-Recognition-test ($p = 0.006$) than CMB-free patients, whereas the findings in Word-List-Recall-test were similar in both groups. Semantic fluency did not significantly differ between both groups. Phonemic fluency was also more impaired in CMB-positive patients ($p = 0.007$). When visuospatial abilities were tested, stroke patients with CMB showed restricted recall of recently learned visual information. No significant differences between the CMB-positive and CMB-free group

were found with respect to TMT A and B. According to their location in the cerebral parenchyma, CMB can be classified as *lobar* or *deep*. When putting only patients in the statistical model showing multilocular CMB, [i.e., CMB in the lobar, cerebellar and/or deep regions ($n = 13$)], the aforementioned significant results became even more apparent (Table 2). Over all, cognitive decline intensified with an increasing number of CMB (mean Pearson's $r = -0.22$).

Discussion

This study yielded the following main findings: (1) within 6 months after ischemic stroke or TIA, CMB-positive patients revealed cognitive decline in more than one cognitive domain; (2) among tested domains, memory and phonemic fluency were most affected in CMB-positive patients, and (3) an occurrence of CMB in more than one of the predefined brain regions was associated with more pronounced cognitive deficits.

A recently published study investigating the long-term effect of CMB on cognitive function showed that EF was most impaired among different cognitive domains in CMB-positive patients 5.7 years after index stroke [15]. The present study also found multiple affected domains in CMB-positive patients; however, in contrast to the other study, memory-associated functions of CMB-positive patients tend to be more impaired compared to that of CMB-free controls. This difference might be due to a more widespread testing of EF [15] and a higher number of CMB in the frontal lobe at baseline examination in the aforementioned study cohort [6]. However, the TMT used in the present study has a high sensitivity to detect EF and, thus, this domain might be indeed less affected in the short-term of CMB-positive stroke survivors.

CMB-positive stroke patients were more cognitively impaired than those without in this study. The exact mechanism underlying cognitive decline in the presence of CMB remains poorly understood and is still a matter of debate [5, 10, 16]. One might argue that CMB located strategically in the brain affect neurons and cause white matter tract disruption which results in an impairment of cerebral networks and distinctive cognitive domains [6]. On the other hand, CMB which represent one type of small vessel disease might only be a measure of severity of cerebral microangiopathy. Thus, CMB may be rather a marker than a direct cause of cognitive decline. In line with this hypothesis, we observed a correlation between cognitive dysfunction and an increasing number of CMB in different cerebral regions, which were in most cases not clustered in a strategic brain area. Our observation is also corroborated by findings of a previously published study that showed an association between cognitive impairment and multiple CMB in widespread areas [5]. A more severe cognitive decline in CMB-positive stroke patients might also be due to a higher vascular lesion load. Akoudad and coworkers reported recently that the association between CMB and cognitive impairment decreased after adjusting for white matter lesions, indicating that CMB might have

Table 2 Results of neuropsychological tests

Neuropsychological sub-tests	Adjusted α-level	*z*-scores			Any CMB+ versus controls *p*-value	Multilocular CMB+ versus controls *p*-value
		Any CMB+	Multilocular CMB+	Control		
Mini-mental status	0.050	−1.73	−2.32	−0.87	0.024*	0.020*
Wordlist learning	0.012	−1.12	−1.93	−0.18	0.009*	0.002*
Wordlist recall	0.012	−0.73	−1.51	−0.87	0.028	0.005*
Wordlist Savings	0.012	−0.42	−0.89	−0.17	0.193	0.227
Wordlist recognition	0.012	−0.87	−1.54	−0.01	0.006*	0.001*
Semantic fluency	0.017	−0.89	−1.3	−0.76	0.296	0.163
Phonemic fluency	0.017	−0.61	−1.05	0.11	0.007*	0.001*
Boston-naming test	0.017	−0.10	−0.22	0.40	0.039	0.072
Constructional praxis	0.017	−0.81	−0.90	−0.57	0.216	0.293
Praxis recall	0.017	−0.77	−1.05	−0.02	0.004*	0.008*
Praxis Savings	0.017	−0.54	−0.69	0.29	0.003*	0.013*
Trail-making test A	0.017	−0.85	−1.24	−0.82	0.296	0.223
Trail-making test B	0.017	−0.72	−0.88	−0.07	0.046	0.143
Trail-making test B/A	0.017	−0.08	0.45	0.32	0.173	0.466

Any CMB+ stroke survivors with at least one detected cerebral microbleed on SWI scans, *multilocular CMB+* stroke patients showing CMB in more than one of the predefined brain regions (i.e., 'lobar', 'cerebellar', and/or 'deep'), *controls* stroke survivors without cerebral microbleeds, *sig* level of significance after Bonferroni's adjustment

only a partial adverse effect on cognition [5]. CMB may originate from cerebral amyloid angiopathy and, thus, are related to Alzheimer disease (AD) [17]. Consequently, more severe cognitive impairment in CMB-positive stroke patients might be due to AD. However, this issue is beyond the scope of the present study, in particular when considering that the contribution of CMB to cognitive impairment in AD remains unclear [18]. Altogether, CMB are probably not a single causal factor of cognitive decline but might accelerate cognitive dysfunction after ischemic stroke.

The study has several limitations: the sample size of the present study is too small to exclude the possibility of spurious findings and to address the possible impact of potential confounders. Furthermore, the design of our study was based on a case–control study (case to control ratio 1:1). Consequently, there is a selection of controls, bearing the risk of a selection bias. Additionally, this case–control study is limited to a restricted number of patients; hence, the study does not represent frequency of CMB-positive patients and stroke survivors without CMBs in the overall stroke population which might affect the results. The design also does not allow providing information on the incidence of CMBs early after stroke. Thus, our findings need to be confirmed in a larger population.

In conclusion, CMB in combination with acute ischemic lesions may increase the risk for cognitive decline of distinct cognitive domains, particularly of phonemic fluency and memory functions, in addition to infarcted cerebral tissue already in the short-term after stroke.

Author Contributions Conceived and designed the study: FF. Performed the study: NC, FF. Analyzed the data: NC, FF, VM. Contributed analysis tools: NC, FF, VM. Wrote the paper: NC, FF, VM.

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Compliance with ethical standards

Conflicts of interest All authors report no disclosures.

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