Original Research Article

Impact of White Matter Lesions on Cognition in Stroke Patients Free from Pre-Stroke Cognitive Impairment: A One-Year Follow-Up Study

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Key Words

Stroke • Cognitive impairment • Cerebrovascular diseases • Degenerative diseases • White matter lesions

Abstract

Background/Aim: Post-stroke cognitive impairment and dementia may be caused by pure vascular, pure degenerative or mixed disease. The relation between post-stroke cognitive impairment and the combination of vascular pathology and degenerative changes is less evaluated. We aimed to evaluate the associations between white matter lesions (WMLs) and patient performance 1 year after stroke on tests of executive functioning, memory and visuospatial function, adjusted for the effects of lifestyle and disease-related factors, including medial temporal lobe atrophy (MTLA). **Methods:** Patients with a first-ever stroke or transient ischemic attack were invited to participate in the study. The associations between the cognitive test performances and WMLs were studied using linear regression [Trail Making Test B (TMT B) and 10-word test] and logistic regression (Clock Drawing Test). **Results:** In total, 199 patients completed the follow-up. The TMT B ($p = 0.029$) and the 10-word test ($p = 0.014$) were significantly associated with WMLs; however, the Clock Drawing Test ($p = 0.19$) was not. The TMT B ($p = 0.018$) and

the 10-word test ($p \leq 0.001$) were both significantly associated with MTLA. **Conclusion:** Impaired executive functioning and memory are significantly associated with WMLs and MTLA. The mechanisms explaining post-stroke cognitive impairment are multifactorial, including different types of vascular pathology and coexisting vascular and degenerative changes.

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Introduction

Stroke is associated with an increased risk of cognitive impairment and dementia [1, 2] and contributes to cognitive decline in various neurodegenerative dementia disorders [3]. Post-stroke cognitive impairment and dementia may be caused by pure vascular disease, pure degenerative disease or the coexistence of vascular and degenerative diseases [4]. In addition to evident stroke lesions, post-stroke vascular changes include subcortical white matter lesions (WMLs), silent lacunar infarctions and cerebral microhemorrhages [5]. WMLs, initially described in 1987 [6] and named leukoaraiosis [7], are defined as areas of high signal intensity on T₂-weighted magnetic resonance imaging (MRI) and are related to variable degrees of demyelination, axonal loss and gliosis [8].

WMLs are associated with vascular risk factors, especially hypertension and higher age [9]. Further, WMLs are associated with the development of vascular and mixed dementia in patients with mild cognitive impairment [10]. Elderly patients with severe WMLs are at risk of becoming more dependent in activities of daily living [11]. Severe post-stroke WMLs predict cognitive decline [12] and indicate a higher risk of recurrent stroke [13]. WMLs are present in 11–21% of adults aged around 64 years [14], in up to 44% of patients with stroke or transient ischemic attack (TIA) and in 50–75% of patients with vascular dementia [15].

Executive and visuospatial dysfunctions are associated with severe WMLs, whereas memory and language dysfunctions are only weakly associated with WMLs [16, 17]. However, the correlation between specific clinical symptoms and the topographical location of WMLs is under debate [18, 19]. The relation between post-stroke cognitive impairment and the combination of vascular pathology and degenerative changes has not been fully examined.

Accordingly, we aimed to evaluate the associations between WMLs and patient performance 1 year after stroke on tests measuring executive functioning, memory and visuospatial function. Results were adjusted for the possible effects of lifestyle and disease-related factors, including medial temporal lobe atrophy (MTLA) as an indicator of possible neurodegenerative disease mechanisms.

Methods

Participants

All patients with a first-ever stroke or TIA admitted to the Stroke Unit of Bærum Hospital, Vestre Viken Hospital Trust between February 2007 and July 2008 were invited to participate in the study. Only those patients who survived the acute phase the first week were assessed. The hospital has a policy of admitting all stroke patients directly to the Stroke Unit. It serves two counties with a total population of approximately 160,000 inhabitants.

We excluded patients with subarachnoid hemorrhage, dementia or mild cognitive impairment diagnosed before stroke onset, a history of cognitive decline or cognitive decline as indicated by a score of ≥ 3.7 on the Informant Questionnaire on Cognitive Decline in the

Elderly (IQ-CODE) [20], previous stroke or TIA, patients who did not speak Norwegian and patients with a remaining life expectancy of less than 1 year as estimated by the treating physician. The IQ-CODE was filled in by the patient's spouse, a first-degree relative or a close friend. The cut off 3.7 was chosen based on the results of a previous study that reported pre-stroke cognitive decline with an IQ-CODE score of ≥ 4.0 [21] and modified to ensure exclusion of pre-stroke dementia.

Assessments

The primary distinction between ischemic stroke and hemorrhagic stroke was based on neuroimaging with cerebral computer tomography (CT). We used the WHO definition of stroke and the clinical diagnosis of TIA based on the acute loss of focal cerebral function with symptoms lasting less than 24 h [22]. TIA patients were included since cognitive impairments in TIA patients may persist beyond the resolution of focal symptoms [23].

Cognitive functioning was measured at baseline and after 12 months using the Mini-Mental State Examination (MMSE) [24], the Clock Drawing Test [25], the Trail Making Test A and B (TMT A and B) [26] and the 10-word test including delayed recall from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (maximal score 40) [27]. The Clock Drawing Test was dichotomized into correct or incorrect answers (5 vs. ≤ 4 according to Shulman [25]). The TMT B was interrupted after 5 min, but we allowed the patients to continue afterwards if they insisted. All patients tried to perform all tests, including the TMT A and TMT B, in the acute phase, but results are only reported from those who were able to complete the tests.

The cognitive assessments were chosen in order to evaluate different cognitive domains. The 10-word test is a measure of memory impairment. The Clock Drawing Test primarily measures visuospatial functions, while the TMT B measures executive functioning. Cognitive impairment of subcortical vascular origin has traditionally been strongly associated with impaired executive functioning, while cognitive impairment of cortical, degenerative origin more often affects episodic memory, visuospatial function and praxis. Although single tests may measure more than one specific cognitive function, we chose a test battery that could assess different cognitive domains.

Neurological impairment was assessed using the National Institutes of Health Stroke Scale (NIHSS) [28]. The neurological examinations were performed on the first day after admittance by an experienced stroke physician. The NIHSS was repeated at discharge and at the 12-month follow-up. We screened for pre-stroke cognitive impairment using the 26-question version of the IQ-CODE [20], repeated after 12 months. Activities of daily living were assessed by the Barthel ADL index [29], and global functioning was evaluated by the modified Rankin Scale [29]. Patients with ischemic stroke were classified according to The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [30] by a stroke physician.

Patients underwent an MRI of the brain at the 12-month follow-up. Cerebral atrophy was measured according to the method first described by Scheltens et al. [31]. Based on the height of the hippocampal formation and the enlargement of the surrounding cerebrospinal fluid spaces, the MTLA is graded from 0 to 4 (MTLA grade 0 = no atrophy; MTLA 4 = highest degree of atrophy; MTLA 0–1 are considered normal values).

WMLs were quantified with a semi-automated method in the Nordic ICE Basis Module as described earlier [32]. The manual placement of regions of interest in known white matter fiber tracks is a common method to measure diffusion parameters. This software is preferred for this purpose, but other programs for diffusion tensor imaging are available [33]. In the fluid-attenuated inversion recovery images, pixel values in the white matter higher than 2 SD above the mean pixel value of the respective slices were defined as WMLs. The total WML areas in all slices were added together and multiplied with the slice thickness to obtain the

total WML volume (ml). In this sample, patients with pencil line lesions along the ventricles and non-confluent small subcortical lesions did not have a total WML volume exceeding 1.5 ml. Moderate and severe lesions may represent subcortical ischemic small vessel disease [16].

Statistics

The associations between the cognitive test performances (outcome variables) and WMLs (explanatory variable) were studied using linear regression (TMT B and 10-word test) and logistic regression (Clock Drawing Test). First, univariate analyses were performed. Second, 19 candidate variables were analyzed as possible confounding variables, i.e. age, sex, Apo E alleles, MTLA, education, vascular risk factors, etiological subtypes of ischemic stroke, neurological deficits as measured by NIHSS and stroke in the left hemisphere (table 2). Only predictors assessed at baseline, except for physical activity which was assessed at the follow-up, were included in the analyses in order to evaluate the effect on cognitive outcomes, WMLs and MTLA 12 month after stroke. All explanatory variables with a p value <0.20 in unadjusted analyses were included in the multivariate regression models. All variables (except for WMLs) with a p value >0.05 were thereafter removed from the models, one at a time, until the final adjusted models were reached. We assessed the interaction between WMLs and MTLA for each outcome using regression models that included WMLs, MTLA and their product as explanatory variables. We used all data available for each analysis, which ranged from n = 148 in multivariable analyses to n = 197 in univariable analyses.

Statistical analyses were performed with STATA 11. All significance tests were two-tailed and performed at the 5% level.

Ethics

The study was approved by the Regional Committee for Ethics in Medical Research and by the Data Protection Authorities. All patients gave their written informed consent before inclusion. First-degree relatives gave consent on behalf of patients with reduced capacity. This procedure was approved by the Ethics Committee.

Results

Baseline Characteristics

After inviting 253 patients, 250 agreed to participate in the study. Of these, 23 were excluded; 12 did not fulfill the inclusion criteria (6 had an IQ-CODE score ≥ 3.7 , 1 did not speak Norwegian, 1 had an infarction in the spinal cord, 1 had suffered a previous TIA, 2 withdrew their consent and 1 patient died before signing the consent) and 11 patients were diagnosed with other disease than stroke.

Of the 227 remaining patients, 174 (76.7%) had a cerebral infarction, 36 (15.8%) had suffered a TIA and 17 (7.5%) were diagnosed with cerebral hemorrhage. Baseline characteristics are listed in table 1.

In total, 199 patients completed the follow-up. Of the 28 patients missing, 19 died and 9 refused to complete the follow-up period. Further, 182 had an MRI for analysis of WMLs and MTLA.

The estimated associations between WMLs and the tests for different cognitive domains, including the potentially confounding variables, are displayed in table 2. The cognitive tests for executive functioning, memory and visuospatial function after 1 year of follow-up were all significantly associated with the degree of WMLs. After fitting multivariable regression models including patients' characteristics, vascular risk factors and stroke characteristics, the associations remained statistically significant between the severity of WMLs and the

Table 1. Patients characteristics at baseline and 12 months

Variable	Baseline (n = 227)	12 months (n = 199)
<i>Demographics</i>		
Male gender	115 (50.7)	
Age, years	72.7 ± 12.2	
Education <9 years	55 (24.2)	
<i>Stroke subtype</i>		
Cerebral infarction	174 (76.7)	
TIA	36 (15.9)	
Cerebral hemorrhage	17 (7.5)	
<i>Risk factors</i>		
Hypertension	135 (59.5)	
Hyperlipidemia	124 (54.6)	
Diabetes	27 (11.9)	
Cigarette smoking (present)	51 (22.5)	
Coronary heart disease	53 (23.3)	
Atrial fibrillation	75 (33.0)	
BMI >25	126 (55.5)	
<i>TOAST classification</i>		
Large vessel disease	24 (11.4)	
Cardioembolic disease	66 (31.4)	
Small vessel disease	66 (31.4)	
Stroke of undetermined etiology	54 (25.7)	
<i>Topography</i>		
Right hemisphere	85 (37.4)	
Left hemisphere	115 (50.7)	
Cerebellum/brain stem	27 (11.9)	
<i>Assessments</i>		
NIHSS score on day 1	4.1 (1.0–5.0)	
NIHSS score at discharge	2.4 (0–2.0)	1.8 (0–1.0)
BI score	20.0 (18.0–20.0)	18.6 (19.0–20.0)
mRS score	1.0 (0–2.0)	1.3 (1.0–2.0)
<i>Cognitive assessments (n)</i>		
IQ-CODE	3.10 ± 0.23 (224)	3.31 ± 0.41 (188)
MMSE	25.66 ± 4.78 (214)	25.86 ± 5.8 (194)
TMT A	74.5 ± 65.0 (192)	63.3 ± 48.9 (185)
TMT B	157.4 ± 94.5 (162)	142.4 ± 86.7 (160)
10 word-test, immediate recall	21.2 ± 7.1 (203)	23.6 ± 8.5 (195)
10 word-test, delayed recall	4.2 ± 2.5 (201)*	5.0 ± 3.1 (195)

Values denote n (%), median (IQR) or mean ± SD.

Hyperlipidemia = Total cholesterol >5 mmol/l or low-density lipoprotein cholesterol >3 mmol/l; Coronary heart disease = previous myocardial infarction or present angina pectoris; BMI = body mass index; IQR = interquartile range; BI = Barthel activities of daily living index; mRS = modified Rankin Scale.

* 15 patients did not complete the delayed recall. This test was introduced a little later in the study.

Table 2. Results of unadjusted and adjusted regression models for all proposed explanatory variables and the three outcomes

Variable	10-word test				TMT B				Clock Drawing Test			
	unadjusted		adjusted (final model)		unadjusted		adjusted (final model)		unadjusted		adjusted (final model)	
	regression coefficients (95% CI)	p value	regression coefficients (95% CI)	p value	regression coefficients (95% CI)	p value	regression coefficients (95% CI)	p value	OR estimate (95% CI)	p value	OR estimate (95% CI)	p value
WMLs	–0.30 (–0.44, –0.17)	<0.001	–0.16 (–0.28, –0.03)	0.014	3.50 (1.83, 5.18)	<0.001	1.75 (0.18, 3.33)	0.029	1.06 (1.02, 1.10)	0.003	1.03 (0.99, 1.07)	0.19
Age	–0.24 (–0.33, –0.14)	<0.001			2.82 (1.80, 3.84)	<0.001	2.09 (0.94, 3.23)	<0.001	1.06 (1.03, 1.09)	<0.001	1.06 (1.02, 1.10)	0.001
Sex (male = 0)	–1.17 (–3.59, 1.25)	0.34			6.12 (–21.5, 33.7)	0.66			3.59 (1.97, 6.55)	<0.001	3.26 (1.62, 6.55)	0.001
Number of Apo E 4 alleles present	overall: p = 0.72				overall: p = 0.10				overall: p = 0.62			
1 vs. 0	–0.85 (–3.80, 2.11)	0.57			–36.7 (–71.3, –2.10)	0.038			0.01 (–0.16, 0.18)	0.89		
2 vs. 0	2.05 (–5.49, 9.60)	0.59			–27.3 (–114, 59.1)	0.53			0.22 (–0.22, 0.66)	0.33		
MTLA (2–4 vs. 0–1)	–6.26 (–8.50, –4.02)	<0.001	–4.51 (–6.67, –2.35)	<0.001	70.9 (44.3, 97.5)	<0.001	33.0 (5.86, 60.1)	0.018	3.76 (1.96, 7.22)	<0.001		
Education (≤9 years = 0)	6.55 (3.73, 9.37)	<0.001	4.83 (2.32, 7.34)	<0.001	–22.3 (–57.5, 12.8)	0.21			0.58 (0.29, 1.16)	0.12		
Homocysteine (μmol/l)	–0.25 (–0.50, –0.009)	0.042			2.45 (–0.41, 5.32)	0.093			1.01 (0.95, 1.07)	0.82		
Hypertension (treated)	–3.07 (–5.51, –0.63)	0.014			30.7 (3.52, 57.9)	0.027			1.65 (0.91, 2.99)	0.10		
Hyperlipidemia	4.57 (2.22, 6.92)	<0.001	2.72 (0.59, 4.85)	0.013	–38.3 (–65.5, –11.2)	0.006			0.82 (0.46, 1.45)	0.49		
Diabetes	–3.84 (–7.63, –0.06)	0.047			63.7 (14.9, 112)	0.011	60.4 (17.2, 104)	0.006	1.61 (0.66, 3.92)	0.29		
Atrial fibrillation (at present)	–1.11 (–3.80, 1.57)	0.41			17.1 (–13.0, 47.2)	0.26			1.00 (0.54, 1.88)	0.99		
Coronary heart disease	–2.23 (–5.06, 0.61)	0.12			45.5 (13.7, 77.3)	0.005			0.86 (0.44, 1.71)	0.68		
Cigarette smoking (at present)	–0.14 (–3.54, 3.26)	0.94			–5.65 (–45.1, 33.8)	0.78			0.83 (0.36, 1.90)	0.65		
BMI	0.20 (–0.11, 0.51)	0.21			–1.47 (–5.22, 2.29)	0.44			0.91 (0.84, 0.98)	0.018		
Physical activity (min/week)	0.007 (0.001, 0.01)	0.017			–0.035 (–0.10, 0.03)	0.27			0.997 (0.995, 0.999)	0.007		
Diagnosis	overall: p = 0.010				overall: p = 0.53				overall: p = 0.13			
TIA vs. infarction	3.63 (0.36, 6.90)	0.030			–20.7 (–57.3, 15.9)	0.27			0.40 (0.16, 0.98)	0.046		
Hemorrhage vs. infarction	–3.93 (–8.17, 0.31)	0.069			0.78 (–53.4, 54.9)	0.98			0.71 (0.25, 2.03)	0.53		
TOAST (small vessel disease = 0)	–2.05 (–4.67, 0.56)	0.12			30.7 (2.20, 59.2)	0.035	32.9 (7.69, 58.0)	0.011	1.15 (0.61, 2.15)	0.67		
NIHSS (score on day 1)	–0.62 (–0.85, –0.38)	<0.001	–0.28 (–0.53, –0.04)	0.017	5.33 (0.54, 10.1)	0.029	5.63 (1.02, 10.2)	0.017	1.15 (1.07, 1.23)	<0.001	1.12 (1.04, 1.22)	0.005
Topographic location (left = 0)	3.06 (0.68, 5.44)	0.012	2.59 (0.58, 4.59)	0.009	–9.21 (–36.4, 18.0)	0.50			1.00 (0.56, 1.77)	1.00		

Apo E = Apolipoprotein E; Hyperlipidemia = total cholesterol >5 mmol/l or low-density lipoprotein cholesterol >3 mmol/l; Coronary heart disease = previous myocardial infarction or present angina pectoris; BMI = body mass index. The values are the regression coefficients for the 10-word test and TMT B (linear regression) and the odds ratio for the Clock Drawing Test (logistic regression).

performances on TMT B ($p = 0.029$) and the 10-word list with immediate recall ($p = 0.014$), but not between WMLs and the Clock Drawing Test ($p = 0.19$) (table 2).

In addition, age ($p < 0.001$), MTLA ($p = 0.018$), diabetes ($p = 0.006$), NIHSS score on day 1 ($p = 0.017$) and small vessel disease as cause of the stroke ($p = 0.011$) were significantly and independently associated with the TMT B, whereas low education ($p < 0.001$), MTLA ($p < 0.001$), hyperlipidemia ($p = 0.011$), NIHSS score on day 1 ($p = 0.023$) and left hemisphere

stroke ($p = 0.012$) were significantly and independently associated with the 10-word test. Failure on the Clock Drawing Test was significantly associated with increasing age ($p = 0.001$), NIHSS score on day 1 ($p = 0.005$) and female sex ($p = 0.001$).

No interaction between WMLs and MTLA was observed for any of the three outcomes (all $p \geq 0.34$), indicating that different processes are involved in atrophy and chronic vascular changes.

Discussion

We found that the cognitive tests for both executive functioning (TMT B) and impaired memory (10-word test) were significantly associated with WMLs. However, the bivariate association between the Clock Drawing Test and WMLs was not statistically significant after adjusting for the influence of increasing age, NIHSS score on day 1 and gender.

The association between deficits in executive functioning and WMLs in stroke patients has been reported earlier [16, 17] and may be due to chronic cerebral small vessel disease with endothelial dysfunction, hypoperfusion and affected blood-brain barrier leading to subsequent cell injury [34, 35]. Furthermore, our results also indicate an association between impaired memory and WMLs after stroke. This contrasts the traditional belief that memory disturbances are less severe in vascular dementia than in Alzheimer's disease [36]. Previous findings regarding non-memory-related cognitive deficits in association with WMLs diverge even more [19], and in stroke patients, impaired memory has been related to reduced temporal lobe functioning [37]. However, vascular changes in the brain can be associated with executive functioning as well as with impaired memory [14, 38], ostensibly due to subcortical damage and a disruption of the pathways between gray and white matter. WMLs are related to more rapid global functional decline [39] and, in the post-stroke situation, may contribute to cognitive decline and progression of cognitive dysfunction. In addition, we observed an association between reduced performance on the 10-word test and stroke in the left hemisphere, indicating cortical damage affecting language and understanding.

Both reduced executive functioning and impaired memory were significantly associated with MTLA, supporting the theory that a degenerative component plays a central role in some patients with post-stroke cognitive impairments [3]. Vascular lesions may amplify the effect of existing degenerative pathology or affect beta-amyloid deposits. Further, MTLA, in addition to subcortical vascular changes, seems strongly related to post-stroke executive dysfunction. Our findings support the assumption that white matter changes, vascular lesions of the brain and Alzheimer's disease pathology coexist and give rise to an increased risk of post-stroke cognitive impairment [13, 40].

We observed an association between some vascular risk factors and cognitive impairment; hyperlipidemia was associated with the 10-word test and diabetes with the TMT B. Midlife high cholesterol increases the risk of Alzheimer's disease later in life [41], represents a well-known risk for vascular disease [42] and may indicate a risk for post-stroke cognitive impairments of both degenerative and vascular origin, whereas diabetes is one of the traditional risks for lacunar infarcts [43].

Surprisingly, hypertension was not associated with any of the cognitive tests. Midlife hypertension is a risk factor for dementia [41] as well as for WMLs [9]. One explanation for our finding may be that we only identified treated hypertension, and the hypertension in our patients was mostly well controlled before the stroke. Treatment of vascular risk factors in patients with cerebrovascular disease may slow the progression of WMLs [44] and, therefore, intensive secondary prevention may contribute to preserve cognitive functioning.

Our study has some limitations. We included patients with TIA, and both the incidence of cognitive impairment and the WML load are lower in these patients. Limitations also include the absence of a measure of silent infarcts, microbleeds and global cortical atrophy. In addition, WMLs were measured only in volume. A more precise topographical description of the lesions could have been even more helpful in understanding the relationship between WMLs and cognitive functioning.

We found that the cognitive tests for both executive functioning (TMT B) and impaired memory (10-word test) were significantly associated with WMLs. There was also a significant association between impaired executive functioning and memory with MTLA. Our findings support the assumption that the mechanisms explaining post-stroke cognitive impairment are multifactorial, including different types of vascular pathology and coexistence of vascular and degenerative changes. The relationship between WMLs and MTLA was not significant.

Clinically, it is of importance to determine which patients are at risk of dementia among those who survive a stroke. The onset of cognitive impairment may be linked to the initial severity of WMLs as well as the pre-stroke degenerative process. This aspect has clinical implications in choosing the most appropriate therapeutic strategy and to start prevention earlier in order to preserve cognition. Treatment requires control of all modifiable risk factors.

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Disclosure Statement

The authors have no conflict of interest.

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