

Severe Cerebral White Matter Hyperintensities Predict Severe Cognitive Decline in Patients With Cerebrovascular Disease History

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Background and Purpose—Cerebral white matter hyperintensities (WMHs) are believed to be the consequence of small vessel disease, and it is uncertain whether their extent predicts the risk of dementia in patients with vascular disease history.

Method—Brain MRI was performed in 226 participants of the PROGRESS study. WMH severity was assessed using a visual rating scale. During follow-up, patients were classified for incident severe cognitive deterioration (including dementia) using standard criteria.

Results—Over 4-year follow-up, the incidence of severe cognitive deterioration ranged from 1.1 to 9.1 per 100 person-years in patients with respectively no or severe WMHs at baseline. In multivariable analysis, incident severe cognitive deterioration was associated with baseline severe WMHs (odds ratio=7.7, $P<0.005$).

Conclusion—Higher WMH load is a strong predictor of dementia and cognitive decline in patients with cerebrovascular disease history. (*Stroke*. 2009;40:2219-2221.)

Key Words: dementia ■ stroke ■ cognitive decline ■ cerebrovascular disorders ■ MRI ■ hypertension

Patients with stroke are at increased risk of dementia with an occurrence rising from 7% 1 year after stroke to 48% after 25 years.¹ Apart from age, risk factors for dementia in stroke patients are not well established.^{1,2}

In elderly subjects without stroke, white matter hyperintensities (WMHs) are frequently seen on cerebral MRI and associated with increased risks of dementia or cognitive decline.³ As well as WMHs being frequently observed in patients with stroke, it is suggested they are more severe in this context than in subjects without stroke.⁴ Moreover, it is uncertain whether WMHs are involved in the causal pathway leading to dementia in stroke patients, despite the evidences that small-vessel disease is associated with vascular dementia.⁵ In the present study, we assessed the predictive value of WMHs in relation to the risk of dementia or severe cognitive decline in patients with a history of stroke or transient ischemic attack (TIA).

Methods

Patients were participants of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS).⁶ Briefly, 6105 participants with a history stroke or TIA within the previous 5 years were recruited in 10 countries, between 1995 and 1997. Patients were

randomly assigned, in a double-blind manner, to continued active treatment or matching placebo. Active treatment comprised a flexible regimen based on perindopril (4 mg daily), with the addition of indapamide (2.5 mg daily; or 2 mg daily in Japan). The rationale for the use of combination therapy (perindopril and indapamide or double placebo) rather than single drug therapy (perindopril or single placebo), wherever possible, was to maximize the fall in blood pressure. Treatment and follow-up continued for an average of 3.9 years.

A MRI substudy was initiated in several French collaborating centers in 1995, the details of which have been described.⁷ The St Antoine ethical committee approved the study, and all patients provided written informed consent. In 10 eligible centers that agreed to participate, 322 patients were randomized, among whom 226 had interpretable MRI within 6 months of randomization. Randomized patients who did not participate ($n=96$) were older and more often women compared to those who participated (data not shown).

Baseline cerebral MRI was performed using 1.0 or 1.5 Tesla scanners according to standardized procedures.⁷ A single trained neuroradiologist assessed all the T2/PD weighted images blinded to clinical data. WMHs were rated using the Scheltens' scale⁸ which provided a 4-categories grade: A, "no lesion"; B "mild"; C "moderate"; D "severe."

At each study wave, cognitive function was assessed using Mini-Mental State Examination (MMSE). During follow-up, a 2-phase screening process was used for the diagnosis of dementia.⁶ Participants were screened positive for "possible dementia" based on

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Table 1. General Characteristics of the Participants at Baseline

	Total Sample n=226	White Matter Hyperintensities Grading*				P Value†
		None n=95	Mild n=59	Moderate n=28	Severe n=44	
Mean age (SD‡)	60.5 (10.8)	56.5 (10.6)	60.2 (9.2)	62.3 (10.9)	68.2 (8.6)	<0.0001
Female gender, %	22.1	21.0	22.0	32.1	18.2	0.55
Mean education level,§ y (SD)	17.7 (4.9)	18.2 (4.7)	17.3 (5.0)	18.8 (6.5)	16.5 (3.9)	0.15
High blood pressure,** %	29.6	24.2	33.9	42.8	27.3	0.23
Antihypertensive treatment intake,†† %	46.9	31.6	54.2	53.6	65.9	0.0007
Mean Barthel index (SD)	49.0 (3.7)	48.8 (4.3)	49.1 (4.1)	48.7 (4.8)	49.6 (1.0)	0.69
Mean MMSE‡‡ (SD)	28.4 (2.3)	28.9 (1.9)	27.8 (2.4)	28.5 (2.1)	28.1 (2.7)	0.02
Active treatment, %	48.7	53.7	52.5	39.3	38.6	0.25
Ischemic stroke subtype, %§§	73.0	73.7	67.8	78.5	75.0	0.71
At least one allele €4, %	25.7	24.1	27.3	25.9	26.8	0.91

*Based on the Scheltens scale.

†Based on chi-square test for categorical variables, analysis of variance for continuous variables.

‡Standard deviation.

§Age leaving school.

**Systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 95 .

††Before randomization.

‡‡MMSE indicates mini mental state examination.

§§Stroke classification for study eligibility.

MMSE score evolution and investigator's judgment.⁶ Information gathered on each screen-positive case was reviewed by a Dementia Adjudication Committee, which categorized participants based on the DSM-IV criteria.⁹

Statistical Analysis

The outcome was the occurrence of dementia or severe cognitive decline (drop of at least 3 points between baseline and last recorded MMSE scores) during follow-up. Between groups differences were analyzed with χ^2 tests or analysis of variance for categorical and continuous variables, respectively. We investigated the effect of WMH severity on dementia or severe cognitive decline risk using logistic regression, adjusted for age, sex, and education level (Model A). In a second step, further adjustments for baseline high blood pressure (systolic BP ≥ 160 or diastolic BP ≥ 95), physical impairment (using Barthel index), antihypertensive drug intake before randomization, baseline MMSE score, and treatment allocation were performed (Model B).

Results

Higher age, lower baseline MMSE score, and use of antihypertensive treatment before randomization were significantly associated with increased WMHs severity (Table 1). During follow-up, 24 subjects became demented or developed severe cognitive decline, 3 of whom also had a recurrent stroke during follow-up. Increasing age, lower education, and lower baseline MMSE were associated with significantly higher rate of dementia or cognitive decline (Table 2).

In multivariable analysis (Table 3), dementia risk over 4-year follow-up was 7.7 times higher (95% CI=2.1 to 28.6) in subjects with severe WMHs compared to those without WMHs at enrolment. After excluding subjects who had a recurrent stroke during follow-up (n=25), the adjusted dementia risk was 11.9 times higher in subjects with severe WMHs at baseline ($P<0.001$) compared to subjects without WMHs. No such association was observed between baseline WMHs severity and risk of recurrent stroke during follow-up.

Finally, from the subsample of patients with baseline severe WMHs who had a 4-year follow-up MRI (n=28), those who had an increase in WMHs load over time (n=12) had an increased risk of severe cognitive decline (OR=9.9, 95% CI=1.3 to 75.3).

Discussion

In this study, severe WMHs at baseline brain MRI are an independent predictor of severe cognitive decline over 4-year follow-up. In addition, among subjects with severe baseline WMH load, it is in those whose WMHs load has worsened over time that dementia risk is significantly increased. Our data suggest that WMH load worsening precipitates the onset

Table 2. Baseline Factors' Associations With Dementia and Severe Cognitive Decline During Follow-Up

Baseline Factors	Dementia or Severe Cognitive Decline		
	No (n=202)	Yes (n=24)	P Value
Female gender, %	20.8	33.3	0.16
Age mean (SD*)	59.9 (10.4)	65.4 (13.0)	0.02
Mean education level,† y (SD)	18.0 (5.0)	15.5 (3.8)	0.02
High blood pressure,‡ %	65.8	70.8	0.62
Treatment antihypertensive,§ %	46.5	50.0	0.75
Trial Active treatment, %	50.0	62.5	0.25
At least one allele €4, %	13.6	27.1	0.17
Mean <i>baseline</i> MMSE** (SD)	28.6 (2.0)	26.6 (3.8)	<0.0001
Mean Barthel index (SD)	49.1 (3.7)	48.5 (5.3)	0.44

*Standard deviation.

†Age leaving school.

‡Systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 95 .

§Before randomization.

**MMSE indicates mini mental state examination.

Table 3. Relative Risk of Dementia and Severe Cognitive Decline During Follow-Up According to White Matter Hyperintensities (WMHs) Severity at Entry

Baseline WMHs Grading	n/N	Risk of Severe Cognitive Decline or Dementia			
		MODEL A*		MODEL B†	
		RR (1)	95% CI	RR (2)	95% CI
No WMHs	4/95	1		1	
Mild or moderate WMHs	7/87	1.6	(0.4–6.0)	1.3	(0.4–5.1)
Severe	13/44	7.7	(2.1–28.6)	7.6	(1.9–31.2)

*RR (1)=Relative risk estimated from logistic regression adjusting for age, gender, schooling years.

†RR (2)=Relative risk estimated from logistic regression adjusting for age, gender, schooling years, baseline MMSE score, baseline Barthel Index, high blood pressure, and antihypertensive drug intake before randomization, and treatment allocation (active vs placebo).

of dementia. The fact that only 3 of the incident severe cognitive decline cases followed a recurrent stroke reinforces the assumption of a strong implication of WMHs in the occurrence of dementia.

This study has limitations because of the sample size as well as the absence of measures of silent infarcts or brain atrophy or stroke location, which could influence the relationship between WMH load and dementia. Compared to population-based studies, baseline WMH prevalence and dementia incidence were lower in our sample. This can be partly explained by the younger age of participants and the “healthy effect” selection at enrollment. In addition, our sample included patients with stroke or TIA, and both dementia incidence and WMH load are lower in TIA patients.

Clinically, it is important to know who is at greater risk of dementia among those who survive a stroke. Our findings show that patients with severe WMH load are at high risk of developing dementia, and we can hypothesize that dementia onset is linked to the initial severity or the worsening of WMH load.

Our findings underline that cerebral small vessels disease should have a bearing on how clinicians choose the most appropriate therapeutic approach. In a previous study, we showed that WMH load worsening was reduced by blood pressure lowering in patients with cerebrovascular disease.⁷ The hypothesis that “reducing WMH load worsening by blood pressure lowering after stroke would decrease the risk of cognitive decline and dementia” needs to be tested in larger randomized controlled trials.

Appendix

PROGRESS MRI Substudy Centers and Investigators

Hôpital d’Angers: Drs H. Brugeilles, P. Lejeune, C. Moreau (Neurology); Dr A. Pasco (Radiology). Hôpital de Caen: Dr S. Iglesias, Pr F. Viader (Neurology); Dr J.M. Constant, Pr P. Courtheoux (Radiology). Hôpital de Grenoble: Dr A. Jaillard, Dr J.M. Besson, Pr M. Hommel (Neurology); Dr S. Grand, Pr J.F. Lebas (Radiology). Hôpital de Lille: Dr C. Lucas, Pr D. Leys (Neurology); Dr X. Leclerc, Pr J.P. Pruvost (Radiology). Hôpital de Maubeuge: Drs V. Neuville, T. Rosolacci (Neurology). Hôpital de Meaux: Drs A. Ameri, F. Chedru (Neurology); Dr P. Bérou (Radiology). Hôpital de Nantes: Drs B. Guillon, G. Hinzelin, Pr Feve (Neurology); Drs E. Auffray, H. Desal, Pr De Kersaint-Gilly (Radiology). Hôpital Saint Antoine and Lariboisière, Paris: Drs V. Biousse, K. Berthet, K. Vahedi, Pr MG. Bousser (Neurology). Hôpital Saint Antoine: Drs V. Bousson, C. Levy, L

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Disclosures

None.

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