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Vascular Care in Patients With Alzheimer Disease With Cerebrovascular Lesions Slows Progression of White Matter Lesions on MRI

The Evaluation of Vascular Care in Alzheimer's Disease (EVA) Study

Edo Richard, MD; Alida A. Gouw, MD, PhD;
Philip Scheltens, MD, PhD; Willem A. van Gool, MD, PhD

Background and Purpose—White matter lesions (WMLs) and cerebral infarcts are common findings in Alzheimer disease and may contribute to dementia severity. WMLs and lacunar infarcts may provide a potential target for intervention strategies. This study assessed whether multicomponent vascular care in patients with Alzheimer disease with cerebrovascular lesions slows progression of WMLs and prevents occurrence of new infarcts.

Methods—A randomized controlled clinical trial, including 123 subjects, compared vascular care with standard care in patients with Alzheimer disease with cerebrovascular lesions on MRI. Progression of WMLs, lacunes, medial temporal lobe atrophy, and global cortical atrophy were semiquantitatively scored after 2-year follow-up.

Results—Sixty-five subjects (36 vascular care, 29 standard care) had a baseline and a follow-up MRI and in 58 subjects, a follow-up scan could not be obtained due to advanced dementia or death. Subjects in the vascular care group had less progression of WMLs as measured with the WML change score (1.4 versus 2.3, $P=0.03$). There was no difference in the number of new lacunes or change in global cortical atrophy or medial temporal lobe atrophy between the 2 groups.

Conclusions—Vascular care in patients with Alzheimer disease with cerebrovascular lesions slows progression of WMLs. Treatment aimed at vascular risk factors in patients with early Alzheimer disease may be beneficial, possibly in an even earlier stage of the disease. (***Stroke***. 2010;41:554-556.)

Key Words: Alzheimer ■ MRI ■ randomized controlled trial ■ vascular risk factors ■ white matter lesions

In addition to medial temporal lobe atrophy (MTLA) and global cortical atrophy (GCA), white matter lesions (WMLs) and (lacunar) infarcts are common findings in Alzheimer disease (AD). Patients with AD with cerebrovascular lesions (CVLs) have fewer plaques and tangles than those without, suggesting that cerebrovascular lesions contribute to the dementia syndrome and its severity. WML increase and new lacunar infarcts occur over time in elderly subjects and patients with AD.[1] Systolic hypertension, being overweight, and having high triglycerides are risk factors for increase of cerebrovascular lesions. Vascular risk factors like hypertension, diabetes, hypercholesterolemia, and being overweight are associated with an increased risk of AD. Treatment of cardiovascular risk factors reduces the risk of stroke and treatment of hypertension reduces the risk of incident dementia, including AD. Whether treatment of hypertension and other cardiovascular risk factors can prevent new vascular lesions in patients with AD is unknown. This study investigates whether an intervention strategy aimed at several vascular risk factors in patients with early AD with CVL can prevent additional WMLs and cerebral infarcts to slow down disease progression.

Methods

Sixty-five patients participating in the Evaluation of Vascular Care in Alzheimer's Disease (EVA) Study, a multicenter randomized controlled clinical trial investigating whether vascular care can slow down dementia progression in patients with early AD with CVL, were included. This study is described in detail elsewhere.[2]

Patients were randomized to vascular care (VC) or standard care (SC). VC consisted of lifestyle interventions (weight loss and dietary advice in case the patient was overweight, physical exercise, smoking cessation) and medication (38 to 100 mg acetylsalicylic acid, 50 mg pyridoxine, and 0.5 mg folic acid). Hypertension ($>140/90$ mm Hg) was treated according to a stepped protocol (reducing salt intake and increasing exercise, diuretic, and, if necessary, a β-blocker or calcium antagonist). Hypercholesterolemia (total cholesterol >5 mmol/L) was treated with 40 mg pravastatin. VC patients were followed 3 monthly to monitor compliance and adjust the interventions when necessary. SC patients were referred back to their general practitioner. A follow-up MRI scan was obtained after 2 years.

Table 1.   Baseline Parameters

Parameter	Standard Care (N=29)	Vascular Care (N=36)	P
Clinical			
Age, mean (SD), years	75.3 (3.9)	76.8 (5.7)	0.24
Sex: female, no. (%)	16 (55.2)	18 (50.0)	0.44
Blood pressure, mm Hg			
Systolic	159.7 (23.7)	151.0 (24.8)	0.15
Diastolic	88.0 (13.5)	80.8 (10.2)	0.02
Total cholesterol, mmol/L	5.6 (1.1)	5.9 (1.4)	0.31
High-density lipoprotein, mmol/L	1.6 (0.6)	1.6 (0.6)	0.91
Low-density lipoprotein, mmol/L	3.3 (1.0)	3.6 (1.1)	0.28
Triglycerides, mmol/L	1.5 (0.9)	1.7 (0.9)	0.51
Homocysteine, μmol/L	14.6 (5.8)	17.4 (13.0)	0.34
Folic acid, nmol/L	15.6 (7.7)	17.3 (9.6)	0.44
Vitamin B12, pmol/L	293.0 (109)	335.0 (159)	0.24
Smoking, no. (%)	0 (0)	2 (5.5)	0.22
Body mass index, kg/m^2 (SD)	27.6 (4.7)	26.0 (4.0)	0.14
Mini-Mental State Examination (SD)	22.8 (3.2)	23.2 (3.4)	0.66
Radiological			
WML Fazekas, no. (%)			
0	0 (0.0)	1 (2.8)	
1	9 (31.0)	13 (36.1)	
2	9 (31.0)	16 (44.4)	0.13
3	11 (37.9)	6 (16.7)	
WML Scheltens, mean (SD)	18.9 (6.5)	17.2 (7.9)	0.36
GCA, n (%)			
0	2 (6.9)	3 (8.6)	
1	16 (55.2)	21 (60.0)	
2	10 (34.5)	10 (28.6)	0.58
3	1 (3.4)	1 (2.9)	
MTLA, mean (SD)	1.7 (0.9)	1.6 (0.8)	
Lacunes, n (%)			
0	19 (65.5)	26 (72.2)	
1–3	9 (31.0)	8 (22.2)	0.62
>3	1 (3.4)	2 (5.6)	
Cortical infarct	2 (6.9)	2 (5.6)	

Primary outcome parameter was the progression of WMLs and the occurrence of new lacunar infarcts. Secondary outcome parameters were progression of GCA and MTLA and the occurrence of new cortical infarcts.

Subjects underwent a standardized MRI scan, including axial fluid-attenuated inversion recovery, T1-weighted 3-dimensional magnetization prepared rapid-acquisition gradient-echo (MPRAGE), and axial or coronal T2-weighted fast spin echo. All scans were analyzed using visual rating scales by a single, trained rater (E.R.) blinded to clinical data and treatment allocation. WMLs at baseline were rated using 2 semiquantitative scales: the Fazekas scale (range, 0 to 4) and the Scheltens scale (range, 0 to 84 points).[3,4] Progression of WMLs was rated with the modified WML change score (range, 0 to 9), scoring stable (0) or increase (1) in 9 regions.[5]

GCA was rated using a 4-point scale and MTLA was rated using a 5-point scale. The intrarater reliability was high (Cohen κ >0.9 for WML, 0.9 for GCA, and 0.8 for MTLA).
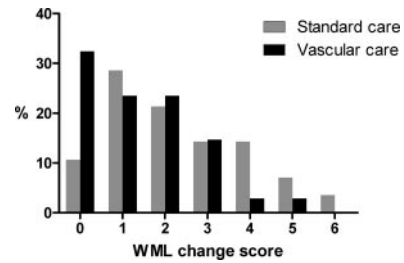

Figure. White matter lesion change score in the SC group and the VC group.

Group differences at baseline were assessed using Student t test, Mann–Whitney U test, and χ^2 or Fisher exact test where appropriate. The modified WML change score was analyzed using Mann–Whitney U statistics and was trichotomized into none, medium (1 to 3 points), or severe (>3 points) and analyzed with χ^2 statistics. Ordinal regression models were used to correct for baseline diastolic blood pressure and WML severity. The occurrence of new lacunes and cortical infarcts and GCA progression were analyzed with Mann–Whitney U and χ^2 statistics. Progression of MTLA was dichotomized (any progression versus no progression) and analyzed using χ^2 statistics.

Results

Of 123 patients in the EVA trial, 65 (29 [51%] SC versus 36 [55%] VC, $P=0.62$) had a follow-up MRI. Reasons for missing follow-up MRI were death (n=11), inability to visit the hospital, or inability to lie still. Subjects without follow-up MRI had more advanced dementia and more WMLs at baseline, but there were no differences between the SC and VC groups at baseline (Table 1). The VC group had less WML progression than the SC group (1.4 [SD 1.63] versus 2.3 (SD 1.63; $P=0.03$) with a significant linear trend ($P=0.009$; Figure; Table 2). Correcting for baseline diastolic blood pressure did not change this effect ($P=0.02$). No correlation was found between baseline severity of WML and modified WML change score in the intervention group (Spearman rho −0.07, $P=0.70$) and when correcting for baseline Scheltens score, the difference in WML change score remained significant ($P=0.03$). There was no difference in new lacunes, new cortical infarcts, MTLA progression, or GCA progression (Table 2).

Discussion

This study shows that a multicomponent intervention aimed at several vascular risk factors, including medical and non-medical interventions, leads to less WML progression in patients with AD with CVL. This effect could potentially influence cognitive decline, because CVL in patients with AD contributes to dementia severity. A possible reason for the lack of a clinical effect of vascular care in this study

Table 2.   MRI Progression of Abnormalities

	Standard Care (n=29)	Vascular Care (n=36)	P
WML change (SD)	2.29 (1.63)	1.41 (1.33)	0.03
New lacunes, no. (%)	7 (25.0)	5 (15.2)	0.26
MTLA progression, no. (%)	19 (65.5)	25 (69.4)	0.79
GCA progression, no. (%)	6 (21.4)	10 (31.3)	0.29

population, as described before,[2] could be that the disease was already too advanced in this group. Although dementia severity was mild in our sample, it is well known that the neuropathological changes predate the clinical symptoms by years and the WMLs were already moderately severe in our sample. Starting a multicomponent intervention aimed at vascular risk factors earlier, in nondemented elderly subjects, might slow down progression (or occurrence) of WMLs in a similar way and help to preserve cognition in elderly subjects.

The small number of lacunes (and larger infarcts) at baseline and at follow-up precludes a conclusion about the effect of the intervention on these parameters. Although hippocampal atrophy and cortical atrophy are associated with elevated blood pressure, no effect on the progression of GCA and MTLA was found. The study was, however, not powered to find such a difference. Although only part of the initial study population underwent an MRI at 2-year follow-up, the 2 groups were well balanced and no differential dropout occurred. The accuracy and intrarater agreement of visual semiquantitative rating of WML is comparably accurate to quantitative measurements and therefore there was no limitation to our study results.

The higher baseline diastolic blood pressure in the SC group does not readily explain the observed difference, because correction for diastolic blood pressure did not change the effect of the intervention.

The results of this study are encouraging for designing new intervention trials aiming at several vascular risk factors at an earlier disease stage or even in subjects who are not demented yet to prevent dementia or slow down cognitive decline in early dementia.[6]

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Disclosures

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