Aortic Atherosclerosis at Middle Age Predicts Cerebral White Matter Lesions in the Elderly

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Background and Purpose—MRI scans of the brains of elderly people frequently show white matter lesions. Clinically, these lesions are associated with cognitive impairment and dementia. A relation between atherosclerosis and white matter lesions was found in some small cross-sectional studies. However, atherosclerosis is a gradual process that starts early in life. We investigated the longitudinal association between aortic atherosclerosis assessed during midlife and late life and cerebral white matter lesions.

Methods—We randomly sampled subjects between 60 and 90 years old from 2 population-based follow-up studies in which subjects had their baseline examinations in 1975 to 1978 (midlife) and in 1990 to 1993 (late life). In 1995 to 1996, subjects underwent 1.5-T MRI scanning; white matter lesions were rated in the deep subcortical and periventricular regions separately. Aortic atherosclerosis was assessed on abdominal radiographs that were obtained from 276 subjects in midlife and 531 subjects in late life.

Results—The presence of aortic atherosclerosis during midlife was significantly associated with the presence of periventricular white matter lesions ≈20 years later (adjusted relative risk, 2.4; 95% CI, 1.2 to 5.0); the relative risks increased linearly with the severity of aortic atherosclerosis. No association was found between midlife aortic atherosclerosis and subcortical white matter lesions (adjusted relative risk, 1.1; 95% CI, 0.5 to 2.3) or between late-life aortic atherosclerosis and white matter lesions.

Conclusions—The pathogenetic process that leads to cerebral periventricular white matter lesions starts already in or before midlife. The critical period for intervention directed at prevention of white matter lesions and its cognitive consequences may be long before these lesions become clinically detectable. **(*Stroke*. 2000;31:425-429.)**

Key Words: cerebrovascular disorders ■ atherosclerosis ■ leukoaraiosis ■ magnetic resonance imaging ■ white matter

Cerebral MRI scans of elderly, nondemented people frequently show white matter lesions.[1–4] There is evidence that white matter lesions are associated with cognitive decline and dementia.[2,5–8] We previously showed an association between atherosclerosis and white matter lesions in a small cross-sectional population-based study among elderly subjects.[9] However, atherosclerosis is a gradual process that starts in the first decades of life, when prevalence of white matter lesions is very low.[10–13] If atherosclerosis early in life is a predictor for white matter lesions in later years, intervention in early life might help prevent white matter lesion–associated cognitive decline and possibly dementia. Aortic calcification observed on an abdominal radiograph is associated with generalized atherosclerosis and has proved to be a good predictor for the development of vascular events at various sites, including the brain.[14–17] Cerebral white matter lesions can be located in the periventricular or the subcortical region. It is not known whether these 2 types of lesions have the same causes. It has been suggested that especially severe periventricular white matter lesions are associated with impaired cognitive performance.[7]

We studied the association between the presence and severity of aortic atherosclerosis assessed during midlife or late life and the later presence of cerebral white matter lesions in the Rotterdam Scan Study.

Subjects and Methods

Study Population

The Rotterdam Scan Study was designed to study determinants and the consequences of cerebral white matter lesions in the elderly. In 1995 to 1996, 1904 subjects between 60 and 90 years old were randomly selected in strata of age (5 years) and sex from 2 large, ongoing, prospective follow-up cohort studies that had their baseline examinations during the subjects' midlife (the Zoetermeer Study) or late life (the Rotterdam Study). The mean age of subjects during

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midlife was 53.7 years (SD, 5.5) and during late life, 68.7 years (SD, 8.0). The Zoetermeer Study had its baseline data collection in 1975 to 1978; the mean follow-up period since then was 19.6 years. The Rotterdam Study had its baseline data collection from 1990 to 1993; the mean follow-up period was 4.8 years. The Zoetermeer Study is a population-based follow-up study among 10 361 subjects between 5 and 91 years old and originally focused on determinants of various chronic diseases. The Rotterdam Study is a population-based prospective follow-up cohort study among 7983 elderly subjects ≥55 years old that focuses on determinants of neurological, cardiovascular, locomotor, and ophthalmological disorders in the elderly. Both studies have been described in detail elsewhere.[18,19]

For the Rotterdam Scan Study, subjects were invited by letter and subsequently contacted by telephone. Upon a subject's agreement to participate in the study, a list of contraindications was reviewed to assess eligibility (dementia; blindness; or presence of MRI contraindications, including prosthetic valves, pacemaker, cerebral aneurysm clips, intraocular metal fragments, cochlear implants, and claustrophobia). Of 1904 invited subjects, 1717 were eligible. Complete information, including a cerebral MRI scan, was obtained from 1077 persons (response, 63%): 563 from the Rotterdam Study (response, 68%) and 514 from the Zoetermeer Study (response, 58%). Each participant signed an informed consent form. The study was approved by the medical ethics committee of Erasmus University.

Measurement of Aortic Atherosclerosis

Abdominal radiographs were taken in subjects ≥45 years old at the time of baseline data collection of the Zoetermeer Study. In 305 of the 401 subjects in our study who were >45 years old at the time of baseline data collection, a lateral abdominal radiograph had been obtained (76%, comparable to the initial response of 82% for abdominal radiographs back in 1975). During the follow-up study (1995 to 1996), 276 of these radiographs could be retrieved. Abdominal radiographs were also obtained during the baseline examination of the Rotterdam Study. An abdominal radiograph had been obtained in 531 of our participants (response, 94%). Aortic atherosclerosis was considered present if calcified deposits were visible as linear densities in an area parallel and anterior to the lumbar spine. The severity of atherosclerosis was rated as mild when deposits were between 0 and 1 cm and as moderate to severe when deposits were ≥1 cm.

Measurement of Other Baseline Covariates

All measurements were done in a similar way at baseline and follow-up in both subpopulations of the Rotterdam Scan Study. Height and weight were measured with the subject without shoes and in light clothing. The body mass index was calculated as weight divided by height squared. Blood pressure was measured 2 times on the right arm by means of a random-zero sphygmomanometer with the subject in the sitting position. The average of these measurements was used. Hypertension was defined as a systolic blood pressure ≥160 mm Hg and/or a diastolic blood pressure ≥95 mm Hg and/or the self-reported use of blood pressure–lowering medication. Information on smoking was obtained through a standardized questionnaire, which was checked by a physician during the interview. Diabetes mellitus was considered present if the participant was taking oral antidiabetics or insulin (both subpopulations) or if the random or postload glucose level was >11.1 mmol/L (subjects originating from the Rotterdam Study).[20] Serum total cholesterol was measured by an automated enzymatic method.[21]

MRI Scanning Protocol

An axial T1-, T2-, and proton density (PD)-weighted cerebral MRI scan was made on a 1.5-T MRI scan in all participants. Subjects recruited from the Zoetermeer Study were scanned with a 1.5-T MR Gyroscan (Philips), and participants from the Rotterdam Study were scanned with a 1.5-T MR Vision (Siemens). To provide comparability, the following pulse sequences were applied: in the Gyroscan, T1 (TR 700 ms, TE 14 ms), T2 (TR 2200 ms, TE 80 ms), and PD (TR 2200 ms, TE 20 ms); and in the Vision, T1 (TR 485 ms, TE 14 ms), T2 (TR 2236 ms, TE 90 ms), and PD (TR 2236 ms, TE 20 ms). Slice thicknesses were 6 and 5 mm, respectively, with an interslice gap of 20.0%. The images were printed on hard copy with a reduction factor of 2.7.

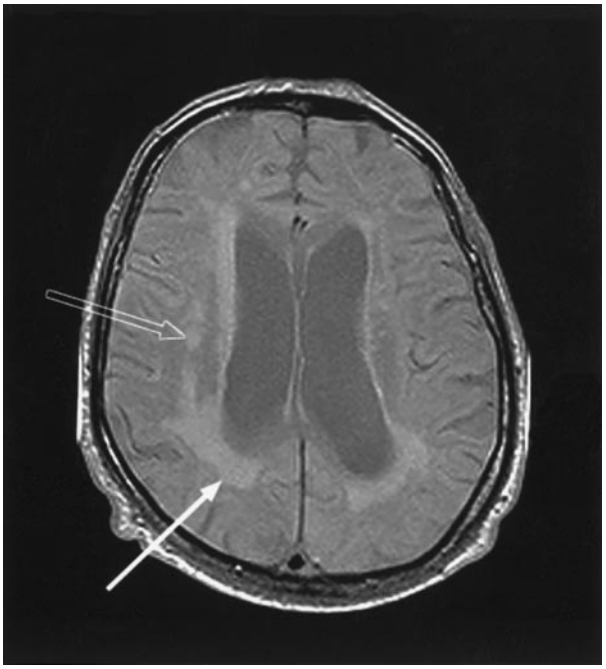

Figure 1. Example of an MRI scan with both periventricular (solid arrow) and deep subcortical (open arrow) white matter lesions.

White Matter Lesion Rating Scale

White matter lesions were considered present if they were visible as hyperintense on both PD- and T2-weighted images and not hypointense on T1-weighted images. White matter lesions were distinguished into those in the deep subcortical and the periventricular regions (Figure 1). The number and size of deep subcortical white matter lesions were rated on hard copy according to their largest diameter in categories of small (<3 mm), medium (3 to 10 mm), or large (>10 mm) lesions. To calculate a deep subcortical white matter lesion volume on hard copy, white matter lesions were considered to be spherical, with a fixed diameter per size category. Periventricular white matter lesions were rated semiquantitatively per region: adjacent to frontal horn (frontal capping), adjacent to lateral wall of lateral ventricles (bands), and adjacent to occipital horn (occipital capping) on a scale ranging from 0 (no white matter lesions), to 1 (pencil-thin periventricular lining), 2 (smooth halo or thick lining), and 3 (large, confluent white matter lesions). The overall degree of periventricular white matter lesions was calculated by adding up the scores for the 3 separate categories (range, 0 to 9).

All MRI scans were examined by 2 raters from a pool of 4 experienced raters. In case of a disagreement of >1 point, a consensus reading was held; in all other cases, the readings of both readers were averaged. The interrater and intrarater studies showed a good to excellent agreement. Weighted κ values for grading the periventricular white matter lesions were between 0.79 and 0.90. For total deep subcortical white matter volume, the interreader and intrarater intraclass correlation coefficients were 0.88 and 0.95, respectively.

Statistical Analysis

The relation between aortic atherosclerosis and white matter lesions was assessed by means of age- and sex-adjusted logistic regression with the presence of severe white matter lesions as the dependent variable. All analyses were also adjusted for the following possible

TABLE 1. Characteristics of Participants in the Rotterdam Scan Study During Midlife (Assessment 1975 to 1978) and Late Life (Assessment 1990 to 1993)

Characteristic	Mid-life Assessment	Late-life Assessment
No. of subjects	276	531
Women, %	57.2	48.8
Mean age, y	53.8 (5.5)	68.7 (8.0)
Mean age at MRI (1995–1996)	73.4 (5.5)	73.4 (7.9)
Body mass index, kg/m^2	25.3 (2.9)	26.3 (3.4)
Systolic blood pressure, mm Hg	133.8 (17.3)	136.7 (20.7)
Diastolic blood pressure, mm Hg	82.4 (10.7)	73.2 (10.8)
Serum cholesterol, mmol/L	6.2 (1.1)	6.7 (1.2)
Aortic atherosclerosis, %	21.0	58.7
Hypertension, %	30.5	38.4
Diabetes mellitus, %	0.3	4.4
Smokers, %		
Current	36.0	20.2
Former	33.2	45.5
Never	30.8	34.3

Values are unadjusted means (SD) or percentages.

baseline confounding factors: body mass index, total serum cholesterol, diabetes mellitus, hypertension, and smoking (never, former, or current). The relative risk (RR), as estimated by the odds ratio, was used to quantify the association. White matter lesions were dichotomized at the upper quintile of their distribution, reflecting the presence of severe white matter lesions. Subjects without severe white matter lesions were the reference group (lower 4 quintiles). The association between midlife and late-life aortic atherosclerosis and presence of white matter lesions was studied by entering aortic atherosclerosis as a dichotomous variable (no versus mild or moderate to severe) into the model. A possible dose-response relation between the severity of aortic atherosclerosis and white matter lesions was studied by creating dummy variables for the extent of aortic atherosclerosis (none, mild, or moderate to severe). The relative risks are presented with a 95% CI.

Results

Table 1 shows the baseline characteristics of the study population. The overall response rate was 63%; it declined from 73% among subjects between 60 and 70 years old to 48% among participants between 80 and 90 years old in 1995 to 1996. Nonparticipants from the original Zoetermeer Study and the original Rotterdam Study were significantly older than participants (75.6 versus 70.8 years, $P<0.001$, and 76.6 versus 73.7 years, $P<0.001$, respectively). There was no significant difference according to sex, diastolic blood pressure, or the prevalence of aortic calcification or hypertension at baseline. Nonparticipants from the Zoetermeer Study had a higher systolic blood pressure (135.3 versus 132.8 mm Hg, $P=0.05$) at baseline compared with participants, whereas this was not significantly different for subjects from the Rotterdam Study.

Prevalence of aortic atherosclerosis was 21% at midlife and 59% at late life. During midlife, 218 subjects had no aortic atherosclerosis, whereas mild and moderate-to-severe aortic atherosclerosis was observed in 24 and 34 subjects, respectively. During late life, 219 subjects had no aortic atherosclerosis, whereas mild and moderate-to-severe aortic atherosclerosis was observed in 113 and 199 subjects, respectively. At follow-up, 20% of all participants were without any periventricular white matter lesions and 8% without subcortical white matter lesions.

Table 2 shows that the presence of aortic atherosclerosis during midlife is significantly associated with the presence of severe periventricular white matter lesions 20 years later (RR, 2.4; 95% CI, 1.2 to 5.0) but not with deep subcortical white matter lesions (RR, 1.1; 95% CI, 0.5 to 2.3). The risk for severe periventricular white matter lesions 20 years later was 2.8 (95% CI, 1.0 to 7.0) for women (n=159) and 2.4 (95% CI, 0.8 to 6.7) for men (n=117). The risk for severe subcortical white matter lesions 20 years later was 1.1 (95% CI, 0.4 to 3.4) and 0.9 (95% CI, 0.3 to 2.7) for women and men, respectively. In contrast, the presence of aortic atherosclerosis during late life was not associated with either type of white matter lesion.

Figure 2 shows a clear relation between the extent of aortic atherosclerosis in midlife and the presence of periventricular white matter lesions 20 years later ($P_{trend}=0.002$). There was no such association with deep subcortical white matter lesions ($P_{trend}=0.68$). For mild and moderate-to-severe aortic

TABLE 2. Relative Risk (95% CI) of Severe White Matter Lesions* Associated With Midlife and Late-Life Aortic Calcification

	Aortic Calcification in Midlife		Aortic Calcification in Late Life	
	Absent	Present	Absent	Present
No. of subjects	218	58	219	312
Periventricular white matter lesions				
Model 1	1.0 (ref)	2.3 (1.2–4.6)	1.0 (ref)	0.9 (0.6–1.4)
Model 2	1.0 (ref)	2.4 (1.2–5.0)	1.0 (ref)	1.0 (0.6–1.6)
Subcortical white matter lesions				
Model 1	1.0 (ref)	1.0 (0.5–2.0)	1.0 (ref)	1.1 (0.6–1.7)
Model 2	1.0 (ref)	1.1 (0.5–2.3)	1.0 (ref)	1.1 (0.6–1.8)

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, baseline presence of diabetes mellitus, hypertension, smoking behavior, serum cholesterol, and body mass index.

*Dichotomized at the upper quintile of the severity distribution of white matter lesions.

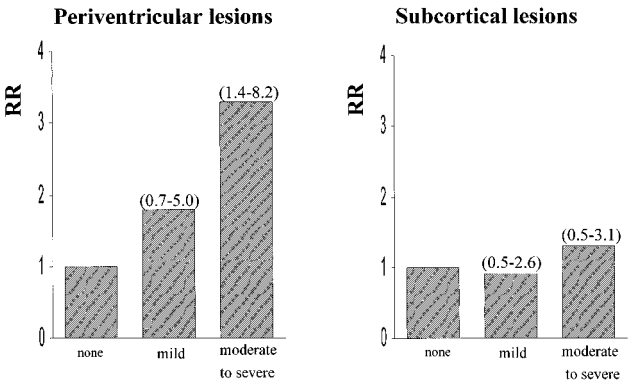

Figure 2. Association between midlife severity of aortic atherosclerosis and presence of severe white matter lesions 20 years later (relative risks, with 95% CI given in parenthesis).

atherosclerosis in late life, the relative risks of having periventricular white matter lesions were 1.0 (95% CI, 0.5 to 1.9) and 0.7 (95% CI, 0.4 to 1.3), and for deep subcortical white matter lesions, 1.2 (95% CI, 0.6 to 2.3) and 0.8 (95% CI, 0.4 to 1.4), respectively. Again, there were no major sex differences in these associations.

Discussion

We found a dose-dependent relation between severity of aortic atherosclerosis during midlife and the presence of periventricular white matter lesions 20 years later. There was no association between the presence of aortic atherosclerosis in late life and white matter lesions. A strength of this study is its large number of elderly participants from the general population, including institutionalized persons. Another important feature is that this study is the first longitudinal study of its kind, with a follow-up of almost 20 years.

Some limitations and methodological issues need to be addressed. The overall response rate was 63%, and this may have led to selection bias, especially among the oldest participants. Still, we consider it unlikely that selection bias has played a major role in our study, because there were only small, nonsignificant, differences between participants and nonparticipants. We cannot exclude the possibility that our relative risks are somewhat underestimated, because we performed our study in survivors of the 2 baseline studies. Subjects who had died between baseline examination and follow-up may have had more severe aortic atherosclerosis than those who survived.

Another limitation is that no neuroimaging was available at baseline of the study. This makes it difficult to provide definitive proof of a temporal relation between aortic atherosclerosis and white matter lesions. As for the validity of radiographic assessment of aortic calcification for the diagnosis of atherosclerosis, an autopsy study showed that radiographically detected aortic calcification represented true intimal atherosclerosis.[14] Compared with CT, it was shown that calcifications seen on the radiograph were in the vessel wall in all cases.[22]

The association between aortic atherosclerosis and cerebral white matter lesions was found only for aortic plaques in midlife and not for those found in late life. The explanation may be that subjects who already had mild or severe aortic atherosclerosis during midlife had progressed to more severe atherosclerosis at the time of the MRI scan than subjects with a similar degree of aortic atherosclerosis at a much higher age. Apparently, it takes many years before atherosclerosis progresses to such a severe stage that it is reflected in the brain. Our finding of a linear relation between severity of aortic atherosclerosis and the presence of white matter lesions supports this interpretation. Another explanation for the weak association between late-life aortic atherosclerosis and white matter lesions might be that in elderly subjects, the presence of atherosclerosis has less discriminative power, because many other risk factors for white matter lesions coexist.

The association between aortic atherosclerosis and white matter lesions was confined to periventricular white matter lesions. This suggests that different pathophysiological processes underlie periventricular and subcortical white matter lesions, possibly related to vascularization. Because the periventricular white matter is an arterial border zone, already marginally perfused under physiological circumstances, it is especially vulnerable to a decrease of cerebral blood flow.[23–25] In contrast, the subcortical white matter is not an arterial watershed area.[26] Atherosclerosis induces hyalinization, tortuosity, and elongation of vessels in the periventricular white matter.[24,27–29] This may contribute to a decrease in blood flow in the periventricular white matter, leading to ischemia.[24] This explanation is supported by studies that found an association between periventricular white matter lesions and atherosclerosis-related factors as hypertension, diabetes mellitus, and the presence of silent infarcts.[30]

In conclusion, our study shows that aortic atherosclerosis during midlife is a major risk factor for periventricular white matter lesions in the brain at greater age. Our results suggest that the presence of atherosclerosis at middle age is already predictive for the presence of white matter lesions later in life. Any therapeutic intervention should therefore preferably take place at the early stages of atherosclerosis.

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