Determinants of cerebral white matter lesions

A longitudinal population based MRI study

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Een longitudinaal bevolkingsonderzoek

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Chapter 1

Introduction

White matter lesions are frequently found on cerebral magnetic resonance imaging scans of elderly non-demented and demented people.[1-4] The pathogenesis of white matter lesions is largely unknown. However age and high diastolic and systolic blood pressure levels and indicators of atherosclerosis have consistently been reported as risk factors for white matter lesions, regardless of their location.[2-5] Many other, especially vascular, risk factors have been associated with white matter lesions, but these relations were mostly not consistent throughout studies.

There is growing evidence that white matter lesions play an important role in the development of cognitive decline and dementia.[4,6-8] The white matter can be distinguished into two separate anatomical regions, namely the periventricular white matter (a strip of white matter adjacent to the lateral ventricles) and the subcortical white matter (the white matter just underneath the gray matter). Only a few studies have distinguished between these two locations and have reported on their determinants separately.[9,10] Yet it may be that different risk factors underlie white matter lesions at different locations, or that lesions in different locations may have different cognitive consequences.

To date, the reported associations came almost exclusively from cross-sectional MRI studies among elderly people. However, the well-established risk factors hypertension and atherosclerosis already occur much earlier in life, when the prevalence of white matter lesions is still low. In order to gain more insight in the pathogenesis of white matter lesions a follow-up study starting at mid-life age would be very informative. In addition to this, many risk factors are more discriminative at younger age (when the prevalence of the risk factor is still low) than at higher ages.

The aim of this thesis is to report on the frequency distribution of white matter lesions in the periventricular and subcortical region in elderly people. Secondly, it addresses the association between vascular determinants (assessed during mid-life and late-life) and cerebral white matter lesions. The studies presented in this thesis are based on the Rotterdam Scan Study, alongitudinal population-based study among 1084 subjects, aged 60-90 years. The study was carried out in 1995-1996. About one half of them (516 subjects) originated from the Zoetermeer Study, which is a prospective population-based study with baseline data-collection in 1975-1978, and a mean follow-up of 20 years. The remaining 568 subjects came from the Rotterdam Study, which is also a prospective population based cohort study with a baseline data-collection in 1990-1993 (mean follow-up 5 years).

In chapter 2.1. the literature is reviewed on the frequency and risk factors of white matter lesions. Chapter 2.2. describes the region-specific frequency distribution of white matter lesions as observed in the Rotter-

dam Scan Study. The association between blood pressure level, its changes over a longer and a shorter period, and white matter lesions is reported in chapter 3.1. Chapter 3.2. deals with the relation between white matter lesions and hypertension, including its duration and management. Chapter 4 is devoted to the association between indicators of atherosclerosis (chapters 4.1. and 4.2.) and atherosclerosis-related disorders (chapter 4.3. and 4.4.) Chapter 5.1. describes the association between the APOE genotype and the presence of white matter lesions. In chapter 6 the methodological strengths and weaknesses of the study are discussed. In addition a pathophysiological model for the emergence of white matter lesions is proposed.

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Chapter 2

Epidemiology of white matter lesions

2.1 Cerebral white matter lesions: frequency and risk factors

Abstract

Cerebral white matter lesions are a common feature on magnetic resonance imaging (MRI) scans of elderly non-demented people. Prevalence ranges from 5% to 100 % in different studies. The pathogenesis of white matter lesions remains unclear although age, hypertension and the presence of cardiovascular disease have been identified as potential risk factors.

In this review methodological issues and known risk factors are reviewed. The focus is on data obtained from large population based MRI studies. It is concluded that the prevalence of white matter lesions increases with age. Hypertension is an established risk factor for the presence of white matter lesions. In addition there is some evidence for associations with other vascular risk factors, including indicators of atherosclerosis, cardiovascular disease, nutrients and ApoE.

Introduction

With the introduction of the computer tomography (CT) scan and the magnetic resonance imaging (MRI) scan it became possible to investigate the living brain and this revealed a number of unexpected phenomena in the cerebral white matter. Both CT and MRI very frequently show white matter lesions in elderly non-demented subjects.[1-6] There is evidence that these subjects suffer from mild cognitive impairment.[4,7,8] In addition, on MRI scans of brains of patients with Alzheimer's disease or vascular dementia white matter lesions are manifold.[6,9-15] It has been suggested that white matter degeneration may play an important role in the pathogenesis of Alzheimer's disease.[16]

White matter lesions on MRI scans are hyper intense on both T2 and PD (proton density) weighted images with no corresponding lesion at a T1 weighted image. On CT scan they are hypo dense. According to their location they are usually distinguished in periventricular and deep subcortical changes. Most rating scales categorize white matter lesions with respect to size.

Mild to moderate periventricular white matter lesions correlate with perivascular demyelinization, gliosis,[17-19] increased extracellular fluid and both smaller and fewer axons.[20,21] The anatomical substrate of the small, punctate deep subcortical white matter lesions observed on MRI scans is mild gliosis,[22] demyelinization[23,24] and dilated perivascular spaces.[22] These punctate changes are not seen at CT scan and are considered by some authors as a different entity than the large white matter lesions[20,22,25] and not important with regard to functional outcome.[26] However, this has never been confirmed in large population based MRI studies. The larger white matter lesions correspond with lacunar infarctions, white matter rarefaction and infarctions[21,23,27] and thickening of arteriolar walls.[21] The etiology of white matter lesions is not yet fully understood, but findings from epidemiologic,[4,7,8,28] anatomic[29] and neuropathologic[18,21,30] studies suggest underlying small vessel disease.

Today data regarding frequency and risk factors of white matter lesions are available from studies on patient series, selected (volunteer) sample and large cross sectional population based samples. Large population based follow up studies are currently planned. This review will mainly discuss results from large population based studies with randomly selected subjects from the general population aged 55 years or over, namely the Cardiovascular Health Study (CHS),[8] the Atherosclerosis Risk in Communities Study (ARIC),[5] the Helsinki Aging Study[31] and the Rotterdam Study.[4,7]

Methodologic considerations

Introduction

The comparability of studies on frequency and risk factors of white matter lesions is limited by substantial differences between studies. These differences concern the selection of the study population, the assessment and operationalization of the outcome variable and the assessment of the putative risk factors.

Study Population

Differences in the size of the study population and selection of subjects contribute to the varying results on frequency of white matter lesions and the strength of associations found between white matter lesions and its determinants. Many studies are small and therefore not able to identify weak, or strong but rare risk factors. Furthermore, they can not approximately adjust for confounding, e.g. by age. Other studies only comprise of highly selected patients or exclude subjects with risk factors known from other studies to be associated with white matter lesions. This selection may strongly bias the results regarding etiologic relations. In studies that sampled their participants randomly from the general population low response may likewise have introduced selection bias.

MRI specifications

An issue which has drawn little attention till now is the difference in field strength and pulse sequences with relation to prevalence. It is suggested that variations in prevalence of white matter lesions are partly explained by the variations of field strength and pulse sequences among the several studies.[26] Until now this has not been formally investigated.

White matter lesions rating scale

In order to interpret and compare results from various studies on the etiology of white matter lesions comparable grading of white matter lesions is important. Until now almost every investigator created an own rating scale. There are three important considerations with respect to white matter lesion scoring: location, size and number.

Location

An important characteristic of white matter lesions is their location. Usually two locations are distinguished, namely periventricular and deep

subcortical. Since it is suggested that both types of white matter lesions may have a different etiology[29] it is essential not to grade them in one and the same category. Still, many studies do not distinguish different locations and score presence, regardless of location, in a more[3-5,7,8,31-33] or less[9,34] detailed way. In addition, deep subcortical and periventricular white matter lesions can be scored per brain region in order to identify possible region-specific risk factors or region specific functional outcome. None of the population based MRI studies that have been published to date distinguished between deep subcortical and periventricular white matter lesions or did a region specific scoring within these areas.

Size

The importance of punctate deep subcortical and pencil thin periventricular white matter lesions is debated and several authors score them in the group without white matter lesions.[9,34,35] Also, presence of white matter lesions is often dichotomized as absent or present,[1,25,34] regardless of size or location. Others do count white matter lesions per size category and per region, however without using this detailed score in their analyses.[36] It is obvious that these considerations directly affect the prevalence of white matter lesions. As for etiologic studies, the definition of the outcome largely influences the power to identify specific determinants and if punctate or pencil thin white matter lesions are not scored it is even impossible to identify risk factors for these types of lesions. When too crude a scale is used, increases in number or extent of white matter lesions may not be detected. The power to study determinants of white matter lesions will therefore be limited.

Number

Another important feature of a white matter lesions rating scale is how it deals with the number of the deep subcortical white matter lesions. Most currently used scales cluster different amounts of white matter lesions above an arbitrarily cut-off number into one, most severe, category.[4,21,36] To date there are no studies that determine risk factors of white matter lesions in linear regression models or in trend analyses. Scoring the amount of white matter lesions would enable the study of a possible dose-response relation or a threshold in the relation between determinant and number of white matter lesions.

Risk factor assessment

A major problem in reviewing risk factors is that they are not uniformly defined across studies, except for age and gender. For many risk factors different criteria are used, e.g. hypertension. Due to limited sample size or

low exposure other risk factors may be grouped in one exposure category, e.g. vascular diseases. By including different risk factors into one exposure category it is not possible to assess the role of a specific risk factor on white matter lesions. In addition this makes it difficult to compare associations found with these risk factors with results from other studies.

All studies thus far are cross sectional in nature. Having the advantage of being carried out relatively quickly, their potential to investigate causality is limited. Usually it can not be assured that the risk factors preceded the occurrence of white matter lesions. Furthermore, risk factors identified in cross sectional studies may be associated with the white matter lesions themselves or with survival of the subjects with the white matter lesions.

Frequency

Prevalence

The reported prevalence of white matter lesions varies considerably among several MRI studies for reasons as discussed above.

Estimates vary from as low as 10%[4] up to 100%.[1-3,5,8,32,33,37,38] Table 1 presents prevalence of white matter lesions in several studies with randomly selected participants from the general population or healthy volunteers.

All authors found a highly significantly increasing prevalence of white matter lesions with increasing age. The Cardiovascular Health Study reported a prevalence of any white matter lesions of about 90% in subjects between 65 and 69 years increasing up to 98% in persons above 80 years of age.[8] The ARIC study showed a prevalence of any white matter lesions of 85% among subjects with a mean age of 62 years. [5] They do not report prevalence per age category. The Rotterdam Study reported a substantial lower prevalence but only considered moderate to severe lesions. They found moderate to severe white matter lesions present in 11% of subjects between 65 and 69 years and in 54% of subjects between 80 and 84 years. These variations are mainly explained by the use of incomparable rating scales and differences in frequency of risk factors for white matter lesions among the participants.

A few studies pointed out sex differences in prevalence and severity of white matter lesions. The Cardiovascular Health Study showed no large differences in prevalence between men and women, but a significantly increased white matter severity among women in all ages, except for subjects between 65 and 69 years. Similarly, in the Rotterdam Study an in-

Table 1
Prevalence and rating scales of cerebral white matter lesions in population based studies and among healthy volunteers from the general population. Prevalence was defined as the proportion of subjects with white matter lesions present on MRI scan, regardless of severity.

Author/Study	Subjects	White matter rating scale	Age	Prevalence
Breteler (4) *The Rotterdam Study*	population based study (n=111)	Combined score deep subcortical white matter lesions and periventricular white matter lesions on a three point scale.	mean age: 73.8yrs. age range: 65-84yrs.	27.0%
Christiansen (33) *The Copenhagen City Heart Study*	healthy volunteers (n=142)	Eleven categories of deep subcortical white matter lesions with respect to number and size.	mean age: not given. age range: 21-80yrs.	21-30yrs:20.0%; 71-80yrs: 100.0%.
Lindgren (35) -	population based study (n=77)	Combined score deep subcortical white matter lesions and periventricular white matter lesions on a three point scale; in addition per location on a four point scale.	mean age: 65.1yrs. age range: 36-95yrs.	62.3%
Ylikoski (31) *The Helsinki Aging Study*	population based study (n=128)	Deep subcortical white matter lesions and periventricular white matter lesions separately (total score 0-48).	mean age: not given. age range: 55-85yrs.	39.0% and 22.0% for periventricular and subcortical white matter lesions, respectively
Longstreth (8) *Cardiovascular Health Study*	population based study (n=3301)	Combined score deep subcortical white matter lesions and periventricular white matter lesions on a ten point scale.	mean age: 70.7yrs. age range: 65yrs.	95.6%
Liao (5) *ARIC study*	population based study (n=1920)	Combined score deep subcortical white matter lesions and periventricular white matter lesions on a ten point scale.	mean age: 62.4yrs. age range: >55yrs.	85.0%

Schmidt (37) *Austrian Stroke Prevention Study*	population based study (n=355)	Combined score deep subcortical white matter lesions and periventricular white matter lesions on a four point scale.	mean age: 62.1yrs. age range: 45-75yrs.	44.8%
Padovani (39) -	healthy volunteers (n=50)	Combined score deep subcortical white matter lesions and periventricular white matter lesions on a four point scale.	mean age: 62.1yrs. age range: not given.	50.0%
Tupler (40) -	healthy volunteers (n=66)	Deep subcortical white matter lesions scored only on a four point scale.	mean age: 61.8yrs. age range: 45-84yrs.	72.7%
Boone (41) -	healthy volunteers (n=100)	Combined volumetric analysis of deep subcortical white matter lesions and periventricular white matter lesions.	mean age: 62.8yrs. age range: 45-83yrs.	54.0%

creased age-specific prevalence and severity of white matter lesions was found among women as compared to men (figure 1).[7]

To date only one study specified age specific prevalence per location. Ylikoski et al reported a prevalence of 21% of periventricular white matter lesions in subjects below 75 years (mean age 64.1 years) increasing to 65% in subjects over 75 years (mean age 82.3 years). The prevalence of deep subcortical white matter lesions was 11% in subjects below 75 years, increasing to 38% in over 75 years.[31]

Incidence

Until now no data on the incidence of white matter lesions have been reported. Large population based follow-up studies in order to detect incidence of white matter lesions are currently being carried out.

Risk factors

Blood pressure

Hypertension and increase in both systolic and diastolic blood pressure have been found to be major risk factors for presence of white matter lesions in almost all studies that investigated this relation.[4,5,8,9,31,35] The

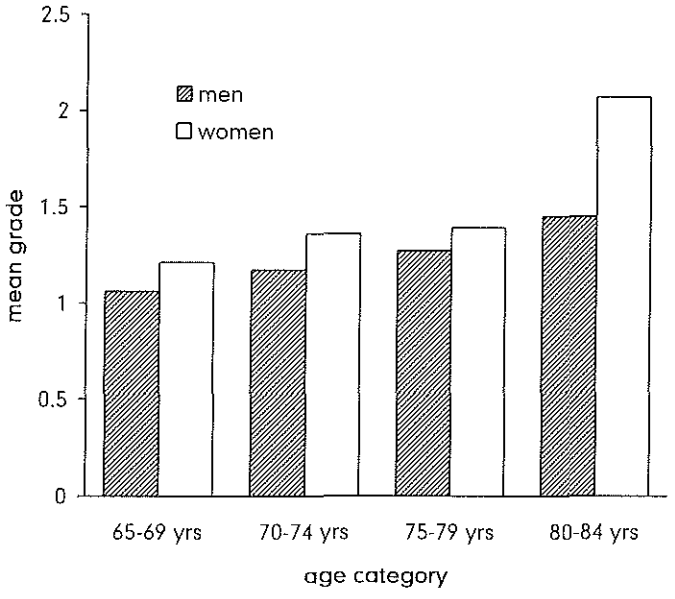

Figure 1
Sex specific severity of white matter lesions – The Rotterdam Study

Rotterdam Study investigated the role of blood pressure in age categories from 65 to 74 years and 75 to 84 years. They found that the association between hypertension, systolic and diastolic blood pressure and presence of white matter lesions was only significant in the youngest age group. In the oldest age group there was a non-significant inverse association between blood pressure and presence of white matter lesions.

The ARIC study looked in great detail at the role of hypertension, its duration, and its treatment and control, on white matter lesions and in different ethnic groups (African and European Americans). Logistic regression was used to estimate odds ratios of having white matter lesions grade ≥3 (range 0-9) as compared to grade <3. Subjects with hypertension had more than twice as often white matter lesions grade ≥3 (OR 2.3; 95%CI 1.7-3.2) and subjects with longer lasting hypertension had a higher risk than subjects with a shorter duration of hypertension (OR 2.5;95%CI 1.8-3.4 and OR 1.7;95%CI 1.0-2.9, respectively). The relation between hypertension and white matter lesions was similar for both ethnic groups. Subjects treated for hypertension, but whose blood pressure did not get under control had the highest risk of white matter lesions grade ≥3 (OR 3.4;95%CI 2.3-5.0), followed by the untreated and the treated subjects whose blood pressure did get under control (OR 2.0;95%CI 1.2-3.1 and OR 1.9;95%CI 1.3-2.9, respectively). Surprisingly, the Helsinki Aging Study found no association between hypertension and white matter lesions. The relation with hypertension or blood pressure levels has not been investigated for periventricular or deep subcortical white matter lesions separately.

Atherosclerosis

Few studies investigated the association between presence of atherosclerosis and white matter lesions.[8,28,42] The Cardiovascular Health Study found in the univariate analyses a significant association between an indicator of intracranial atherosclerosis, intima media thickness of the internal carotid artery wall, and presence of white matter lesions. They found no association with the ankle-to-brachial index, as an indicator of peripheral atherosclerosis.[42] They did not investigate these associations in multivariate models. Results from the Rotterdam Study[28] showed that an increased intima media thickness was associated with increased presence of white matter lesions (OR 1.5;95%CI 1.1-2.1, per 100μm increase) and that the presence of plaques in the carotid artery wall (another indicator of intracranial atherosclerosis) was associated with the presence of white matter lesions (OR 3.9;95%CI 1.0-14.5). In addition they showed an inverse relation between ankle-to-brachial index and severity of white mat-

ter lesions. Fazekas et al.[9] and Lindgren et al.[35] also investigated the role of intracranial atherosclerosis and white matter disease. In rather small population based samples they were not able to show an association between stenosis of the extra cranial carotid artery and presence of white matter lesions. Many studies have confirmed the relation between hypertension and presence of white matter lesions, but the mechanism by which hypertension exerts its action on the cerebral white matter is not known.[4,5,8,9,31,35]

Neuropathological research suggests an important role of blood pressure and hypertension in the pathogenesis of atherosclerosis.[18,22] In order to find out whether atherosclerosis has an independent effect on the occurrence of white matter lesions or is an intermediate between hypertension and white matter lesions, analyses should be performed within strata of atherosclerosis.

In none of the studies described above this stratification was performed.

Diabetes mellitus

Many studies investigated the relation between diabetes mellitus and presence of white matter lesions,[4,5,8,9,31,32] but only a few, relatively small studies, showed an association between diabetes mellitus and presence of white matter lesions.[2,31,43] There is extensive evidence that diabetes mellitus is a risk factor for cardiovascular disease. It has been suggested that this is mediated by an increased degree of atherosclerosis.[44] In a large population based study serum level glucose and the prevalence of diabetes mellitus was significantly associated with indicators of atherosclerosis such as atherosclerotic plaques in the carotid arteries and ankle-to-brachial index.[45]

Fibrinogen

Fibrinogen is strongly associated with preclinical atherosclerosis and also with other cardiovascular risk factors.[46-48] Elevated fibrinogen levels have been reported in subjects suffering from Binswanger's disease. Results from the Rotterdam Study showed an association between increased plasma fibrinogen levels and presence of white matter lesions.[4] In the Cardiovascular Health Study a similar association was found.[8] It is yet unclear whether this elevated fibrinogen level is causally related to the white matter lesions, or is merely the consequence of the underlying small vessel disease.

Cholesterol

Cholesterol is a well-established risk factor for cardiovascular disease and mortality. By accumulating in the arterial wall it plays an important role in the pathogenesis of atherosclerosis. Quite a few studies[3,4,8,28,39,42] addressed whether cholesterol levels were associated with presence of white matter lesions. Longstreth et al were the only ones who found an association with low density lipoprotein (LDL) cholesterol and presence of white matter lesions.[8] In the Rotterdam Study an association between increase in cholesterol and presence of white matter lesions was found in subjects between 65 and 74 years (OR 2.2;95%CI 1.0-4.7), but not in subjects aged 75 years or over.[4]

Smoking

The relation between smoking and white matter lesions has been investigated in few studies.[4,8,35] In the Cardiovascular Health Study subjects were divided into ever smokers versus never smokers. Ever smokers had a significantly higher prevalence of white matter lesions than never smokers.[42] In the Rotterdam Study no significant association between smoking and presence of white matter lesions was found.[4]

Cardiac disease

The role of cardiac disease in the pathogenesis of white matter lesions is unclear. A major reason is that in most studies all kinds of different cardiac diseases (such as coronary heart disease, left ventricular hypertrophy and arrhythmias) are categorized in one group in the analyses.[2,9,35,39] The Cardiovascular Health Study did not show an association between cardiac disease and presence of white matter lesions.[8] In the Rotterdam Study a significant association between a history of myocardial infarction and presence of white matter lesions was found (OR 3.9;95%CI 1.1-14.1).[4] Ylikoski et al reported that subjects with cardiac arrhythmias had an increased risk of deep subcortical white matter lesions (OR 4.0;95%CI 1.0-15.5), but not of periventricular white matter lesions.[31]

History of stroke

Findings from the Cardiovascular Health Study showed that a history of stroke is a very strong determinant of white matter lesions.[8] These results are in congruence with data from the Rotterdam Study,[4] although in that study presence of stroke was analyzed together with presence of myocardial infarction as one variable (OR 4.4;95%CI 1.4-13.7). In contrast, Schmidt et al.[2] showed that prior stroke is not associated with presence of

white matter lesions, but is associated with *severity* of white matter lesions.

The most likely explanation for the association between a history of stroke and the presence of white matter lesions is that the risk factors for both stroke and for presence of white matter lesions largely overlap.

Anti-oxidants

The association between serum anti-oxidants and presence of white matter lesions has thus far only been investigated in the Austrian Stroke Prevention Study.[37] In this selected population based study (response 28%) among 355 participants they showed that subjects with an alpha tocopherol level in the lowest quartile versus subjects in the highest quartile had an OR of 3.7 (95%CI, 1.69 to 8.1) of having severe white matter lesions. This was the only significant association between an anti-oxidant (from a panel of ten) with presence of white matter lesions. From fundamental research it is known that, among other factors, the release of free radicals leads to neuronal damage after cerebral ischemia. An attractive hypothesis is that ischemic damage can be attenuated by so called free radical scavengers, such as antioxidants. Results from large population based studies are needed to confirm or reject these findings.

Alcohol

There is only one study that reported the relation between alcohol consumption and presence of white matter lesions. Among 50 healthy volunteers the authors found no association between alcohol intake and white matter lesions.[39]

Apolipoprotein E gene

Few studies investigated the association between the ApoE genotype and presence of white matter lesions.[49,50] The ApoE gene product is a 34 KD protein, which has an important function in the transportation of lipids and plays a role in repair of damaged (neuronal) membranes. Previous studies have shown an association between the ApoE*4 allele and atherosclerosis. In the CHS ApoE4 carriers had no increased prevalence of white matter lesions.[49] In contrast, Schmidt et al. found an increased risk among ApoE*2 carriers for 'microangiopathy related cerebral damage' (white matter lesions and lacunar infarctions).[50] The authors suggested that the ApoE*2 allele is associated with impaired repair mechanisms. However, due to a low response rate, selection bias may have played a role in this study. Moreover, two different outcome measures (white mat-

ter lesions and silent infarctions) with a probably different pathogenesis were considered as one outcome variable

Ethnicity

Currently there are two large studies in the United States, the ARIC study and the Cardiovascular Health Study in which the relation between ethnicity and white matter lesions was studied.[5,8] Both studies found that African Americans had more white matter lesions than European Americans. The ARIC study investigated this relation in greater detail and showed that this elevated risk could be explained through higher mean systolic and diastolic blood pressure levels among African Americans. When in the model systolic and diastolic blood pressure were introduced the association between white matter lesions and ethnicity was not significant anymore.[5]

Conclusion and recommendations for future research

Most studies showed an increase in prevalence of white matter lesions with increasing age. Gender differences have been reported in some studies but this needs further confirmation. Many studies confirmed the association between hypertension and white matter lesions. Various other risk factors have been investigated. Although several vascular risk factors seem associated, the results from the diverse studies are not unequivocal. For some other vascular determinants, as atherosclerosis, it is not clear whether it is in the causal chain between hypertension and white matter lesions or it is a separate risk factor for presence of white matter lesions.

A major problem in comparing results from various studies is that they are methodologically very different. To yield unbiased estimates of prevalence, incidence and determinants of white matter lesions, future studies should preferably be population based, prospective, not too small, use few exclusion criteria and have a high response. Large incidence studies are needed to investigate the etiology of white matter lesions. They should use similar rating scales in order to enable the comparison of results between studies. The periventricular and deep subcortical white matter have a different arterial supply and there is some evidence that periventricular white matter lesions have different risk factors than deep subcortical white matter lesions.[31] Besides it is unclear whether the small or large sized white matter lesions have the same etiology. Therefore fu-

ture studies should use a rating scale which scores white matter lesions per region and per size.

In order to compare the strength of an association between a risk factor and white matter lesions between studies standardization of risk factor definitions is required. There are a number of putative risk factors that need to be confirmed. Other specific risk factors may be selected for investigation on the basis of plausible etiologic hypothesis and with the aim to elucidate the underlying pathophysiologic mechanism of white matter lesions emergence.

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2.2 Sex difference in the prevalence of cerebral white matter lesions

Abstract

White matter lesions are frequently observed on MRI scans of elderly non-demented and demented people. They are attributed to degenerative changes of small vessels and are implicated in the pathogenesis of cognitive decline and dementia. There is evidence that especially periventricular white matter lesions are related to cognitive decline, whereas subcortical white matter lesions may be related to late-onset depression. We report the frequency distribution of subcortical and periventricular white matter lesions, according to age and gender. We randomly sampled 1084 subjects aged between 60-90 years from the general population. All subjects underwent 1.5T MRI-scanning; white matter lesions were rated separately for the subcortical region and the periventricular region. Of all subjects 8 percent were completely free of subcortical white matter lesions, 20 percent had no periventricular white matter lesions and 5 percent had no white matter lesions in either of these locations. The proportion with white matter lesions increased with age, similarly for men and women. Women had more subcortical white matter lesions than men (total volume 1.45 ml versus *1.29 ml; p=0.33), mainly caused by marked differences in the frontal white matter lesion volume (0.89 ml* versus *0.70 ml; p=0.08). Periventricular white matter lesions were also more frequent among women than men (mean grade 2.5* versus *2.3; p=0.07). Also severe degrees of subcortical white matter lesions were more common in women than in men (OR 1.1; 95% CI 0.8-1.5) and*

periventricular white matter lesions (OR 1.2; 95% CI 0.9-1.7), albeit not statistically significant. In conclusion, the prevalence and the degree of cerebral white matter lesions increased with age. Women had a higher degree of white matter lesions than men. This may underlie the observation of a higher incidence of dementia in women than in men, particularly at later age.

Introduction

White matter lesions are frequently observed on MRI scans of elderly people, they are attributed to degenerative changes of long penetrating arteries.[1-6] Reported prevalence ranges from 5 to 90 percent, depending on study design, study population and rating scales.[1-4,7-9] There is evidence that especially periventricular white matter lesions are related to cognitive decline,[10] whereas subcortical white matter lesions may be related with late-onset depression.[11] White matter lesions can be distinguished into those in the subcortical and in the periventricular region. Only a few studies consider lesions in these regions separately,[12-14] but some based their analysis on a summary score of subcortical and periventricular white matter lesions,[14] as in other studies.[1-3] Although it is well established that the prevalence of white matter lesions increases with age, little is known about site specific frequency, including possible differences between the subcortical and periventricular region, and the lobar location of the lesions. This distinction may be of potential interest since the subcortical and periventricular white matter lesions might have a different pathogenesis and may result in different cognitive or motor consequences. Some studies reported a higher prevalence of white matter lesions among women then men.[1-3] The differences were however not statistically significant, and were only reported for total white matter lesions.

From a population-based sample of subjects over 60 years of age, we report the age and sex specific frequency distribution of either type of white matter lesions by lobar location.

Materials and methods

Study population

The Rotterdam Scan Study was designed to study determinants and cognitive consequences of age related brain abnormalities in the elderly. In 1995-1996, 1904 subjects aged between 60-90 years were randomly selected in strata of age (5 years) and sex from two large ongoing prospective

follow-up cohort studies, the Zoetermeer Study and the Rotterdam Study. Both studies have been described in detail elsewhere.[15,16] In short, the Zoetermeer Study is a prospective population based study among 10361 subjects, aged between 5-91 years at baseline, which studies determinants of chronic diseases. The Rotterdam Study is a population based prospective cohort study, among 7983 elderly subjects aged 55 years and over, which studies determinants of neurological, cardiovascular, locomotor and ophthalmologic diseases in the elderly.

For the Rotterdam Scan Study subjects were invited by a letter, and subsequently contacted by telephone. Upon agreement to participate a list of contraindications was reviewed in order to assess eligibility (dementia; blindness; or presence of MRI contraindications, including prosthetic valves, pacemaker, cerebral aneurysm clips, a history of intra ocular metal fragments, cochlear implants and claustrophobia). From 1904 invited subjects 1724 were eligible. Complete information was obtained, including a cerebral MRI scan, from 1084 persons (response rate 63 percent; 568 from the Rotterdam Study and 516 from the Zoetermeer Study). Each participant signed an informed consent form. The study was approved by the medical ethics committee of Erasmus University Rotterdam, The Netherlands.

MRI Scanning protocol

In all participants an axial T1, T2 and Proton Density (PD) weighted cerebral MRI scan was made on a 1.5T MRI scan. Subjects recruited from the Zoetermeer Study were scanned with a 1.5T MR Gyroscan (Philips, Best, The Netherlands) and participants from the Rotterdam Study were scanned with a 1.5T MR VISION (Siemens, Erlangen, Germany). In order to provide comparability the following pulse sequences were applied: at the Gyroscan T1 (TR 485 ms, TE 14 ms), T2 (TR 2236, TE 90 ms) and PD (TR 2236 ms, TE 20 ms); and at the VISION: T1 (TR 700 ms, TE 14 ms), T2 (TR 2200 ms, TE 80 ms) and PD (TR 2200 ms, TE 20 ms) Slice thickness was 6 mm and 5 mm respectively, with an inter-slice gap of 20.0 percent. The images were printed on hard copy with a reduction factor of 2.7.

White matter lesions rating scale

White matter lesions were considered present if these were hyper-intense on both PD and T2 weighted images and not hypo-intense on T1 weighted images. White matter lesions were distinguished into those in the subcortical and periventricular region. The number and size of subcortical white matter lesions was rated on hard copy according to their largest diameter

in categories of small (<3 mm), medium (3-10 mm) or large lesions (>10 mm). In order to calculate the volume of subcortical white matter lesions on hard copy, they were considered to be spherical with a fixed diameter per size category (range 0-29.5 ml.). Periventricular white matter lesions were rated semi-quantitatively per region: adjacent to the frontal horns (frontal capping); adjacent to the lateral wall of lateral ventricles (bands), and adjacent to the occipital horns (occipital capping), on a scale ranging from 0 to 3. The overall degree of periventricular white matter lesions was calculated by adding up the scores for the three separate categories (range 0-9). White matter lesions could be rated for all subjects except in two individuals in whom the quality of the MRI scan did not allow reliable rating of the subcortical white matter lesions. All MRI scans were examined by two raters from a pool of four experienced raters. In case of a disagreement of more than one point, a consensus reading was held; in all other cases the readings of both readers were averaged. The inter- and intra-rater studies showed a good to excellent agreement. Weighted kappas for grading the periventricular white matter were between 0.79-0.90. For total subcortical white matter volume the inter- and intra-rater intraclass correlation coefficient was 0.88 and 0.95, respectively.

Statistical analyses

The prevalence of white matter lesions was defined as the presence of any white matter lesion (regardless of size or location) in the brain. The relation between the prevalence of white matter lesions and age was assessed by means of age and sex adjusted linear regression analyses. The frequency distribution of either type of white matter lesions was calculated by 10 years age strata (60-70, 70-80 and 80-90 years). The relation between sex and white matter lesions was assessed by means of age adjusted linear regression with white matter lesions as the dependent variable. Analysis of covariance was performed to obtain sex specific mean volume of subcortical white matter lesions per 10 years age stratum or the mean grade of the periventricular white matter lesions. Sex differences for each category (0,1,2 and 3) of periventricular white matter lesions, per region, were analyzed with the Chi-Square test. There is increasing evidence that there exists a dose dependent relationship between severity of white matter lesions and cognitive consequences[1,2] and that especially the presence of severe white matter lesions is associated with a reduced cognitive function.[10,17] We therefore separately analyzed severe subcortical and periventricular white matter lesions per sex by means of an age corrected logistic regression model. White matter lesions were dichotomized at the upper quintile of their distribution, which reflects severe white

matter lesions. The associations are presented as odds ratios with a 95 percent confidence interval (OR; 95%CI)

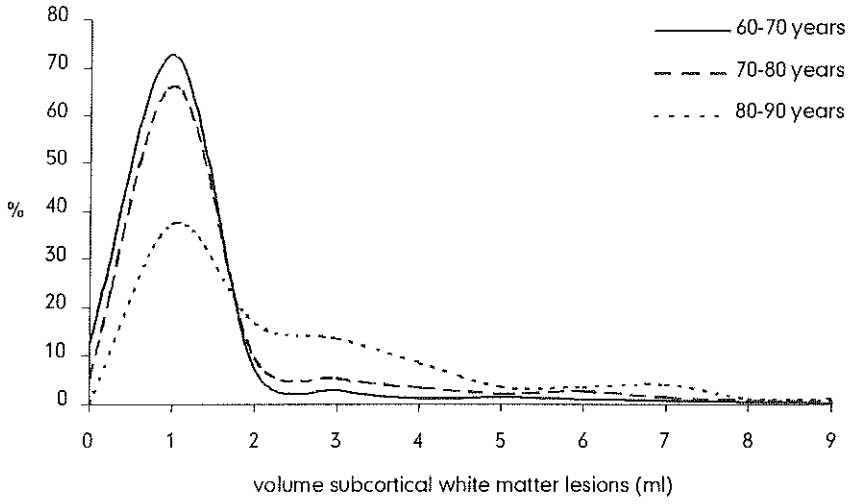

Figure 1a
Distribution of subcortical white matter lesions by 10 year age category

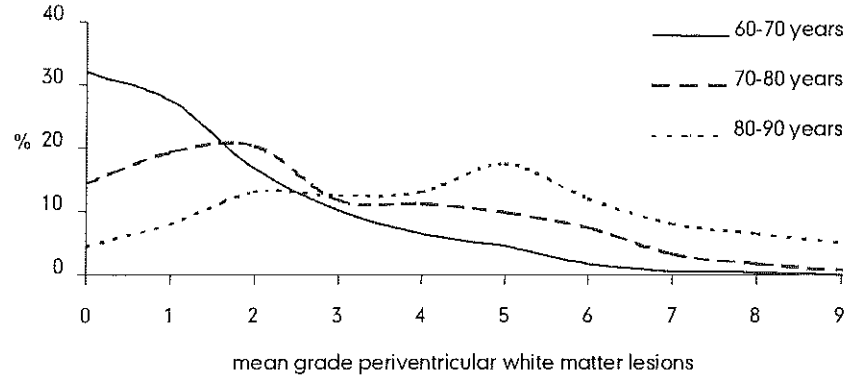

Figure 1b
Distribution of periventricular white matter lesions by 10 year age category

Results

The overall response rate was 63 percent; it decreased with age from 73 percent in subjects aged between 60-70 years to 48 percent in participants aged between 80-90 years. Responders were therefore significantly younger than non-responders (mean age 72.4 years versus 75.9 years, $p<0.001$), whereas there was no sex difference.

In our study 8 percent of all subjects were completely free of subcortical white matter lesions, 20 percent had no periventricular white matter lesions and 5 percent had no white matter lesions in either of these locations. Frequency of white matter lesions strongly depended on age (figure 1). Of subjects aged between 60-70 years, about 13 percent were completely free of subcortical white matter lesions and 32 percent was free of periventricular matter lesions, whereas for subjects aged between 80-90 years these percentages were 0 and 5, respectively. This age effect was similar for men and women. The prevalence of subcortical and periventricular white matter lesions significantly increased with 0.2 percent and 0.4 percent per year, respectively.

Table 1 shows the volume of subcortical white matter lesions per 10 years age stratum by sex. The mean volume of subcortical white matter lesions was highest in the frontal lobe, followed by the parietal, occipital and temporal lobes. This applied to both sexes and all age groups. The mean volume of subcortical white matter lesions increased from 0.6 ml (SE 0.1) for subjects between 60-70 years of age to 3.2 ml. (SE 0.4) for individuals aged between 80-90 years ($p <0.01$). Women had greater volumes of subcortical white matter lesions than men (total volume 1.45 ml *versus* 1.29; $p=0.33$), mainly caused by differences in the volume of frontal white matter lesions (0.89 ml *versus* 0.70; $p=0.08$).

Table 2 shows sex-specific mean grades of periventricular white matter lesions per 10 years category. The mean grade of periventricular white matter lesions increased from 1.5 (SE 0.1) for subjects between 60-70 years of age to 2.4 (SE 0.1) for individuals aged between 80-90 years ($p <0.01$). The mean grade of the total periventricular white matter lesions was higher among women than men (2.5 (SE 0.1) *versus* 2.3 (SE 0.1); $p=0.07$), mainly caused by the significant difference in severity of frontal capping between men and women in all age categories.

Table 3 shows the proportion of subjects with different degrees of periventricular white matter lesions for each of the three different locations per 10 years age-stratum. For all age categories and at every location, proportionally more women than men had the most severe periventricular white matter lesions.

Table 1
Mean volume of subcortical white matter lesions per lobar location per 10 years age stratum.*

Lobar location	60-70 years (n=465)		70-80 years (n=417)		80-90 years (n=200)		overall (n=1082)	
	men (n=226)	women (n=239)	men (n=203)	women (n=214)	men (n=94)	women (n=106)	men (n=523)	women (n=559)
Frontal	0.23 (0.06)	0.43 (0.06)†	0.75 (0.12)	0.90 (0.12)	1.71 (0.31)	1.92 (0.29)	0.70 (0.08)	0.89 (0.07)
Parietal	0.25 (0.05)	0.26 (0.05)	0.50 (0.07)	0.45 (0.06)	1.25 (0.17)	1.23 (0.17)	0.53 (0.05)	0.51 (0.04)
Occipital	0.01 (0.01)	0.02 (0.01)	0.05 (0.02)	0.02 (0.02)	0.16 (0.05)	0.12 (0.04)	0.05 (0.01)	0.04 (0.01)
Temporal	0.00 (0.00)	0.00 (0.00)	0.01 (0.02)	0.00 (0.00)	0.05 (0.02)	0.02 (0.02)	0.01 (0.00)	0.01 (0.00)
Whole brain	0.49 (0.10)	0.72 (0.10)	1.31 (0.18)	1.38 (0.18)	3.18 (0.48)	3.31 (0.44)	1.29 (0.12)	1.45 (0.12)

* Expressed as milliliter white matter lesion volume on hard copy (SE)
† $P < 0.05$

Table 2
Sex specific mean grade of periventricular white matter lesions per region per 10 years age stratum.*

Lobar location	60-70 years (n=466)		70-80 years (n=418)		80-90 years (n=200)		overall (n=1084)	
	men (n=226)	women (n=240)	men (n=204)	women (n=214)	men (n=94)	women (n=106)	men (n=524)	women (n=560)
Frontal capping	0.5 (0.0)	0.6 (0.0)†	0.8 (0.1)	1.0 (0.1)‡	1.3 (0.1)	1.5 (0.1)†	0.8 (0.0)	0.9 (0.0)‡
Bands	0.6 (0.0)	0.5 (0.0)	0.9 (0.1)	1.0 (0.1)	1.4 (0.1)	1.5 (0.1)	0.8 (0.0)	0.9 (0.0)
Occipital capping	0.3 (0.1)	0.3 (0.1)	0.7 (0.1)	0.8 (0.1)	1.4 (0.1)	1.4 (0.1)	0.7 (0.0)	0.7 (0.0)
Total periventricular	1.4 (0.1)	1.5 (0.1)	2,4 (0.1)	2.8 (0.1)	4.1 (0.2)	4.4 (0.2)	2.3 (0.1)	2.5 (0.1)

* Expressed as mean grade (SE)
† $P < 0.05$
‡ $p<0.01$

Table 3
Sex specific frequency distribution of periventricular white matter lesions grades per region per 10 years age-stratum.

Location	Grade	60-70 years		70-80 years		80-90 years		overall	
		men (n=226)	women (n=240)	men (n=204)	women (n=214)	men (n=94)	women (n=106)	men (n=524)	women (n=560)
Frontal capping	0	50.0	42.4	29.9	22.9	14.9	8.5	35.9	28.5
	1	40.6	41.7	43.1	42.0	39.4	31.1	41.4	39.8
	2	8.9	14.6	25.5	33.2	40.4	51.9	21.0	28.8
	3	0.5	1.3	1.5	1.9	5.3	8.5	1.7	2.9*
Bands	0	43.8	46.2	27.0	25.7	8.5	10.4	30.9	31.6
	1	45.6	43.8	51.0	45.8	43.6	35.8	47.3	43.1
	2	9.7	8.3	18.6	21.0	30.9	34.9	17.0	18.2
	3	0.9	1.7	3.4	7.5	17.0	18.9	4.8	7.1
Occipital capping	0	71.7	72.4	48.2	42.5	25.6	23.6	54.2	51.8
	1	20.8	18.8	27.9	32.7	22.3	29.2	23.9	26.1
	2	6.2	7.1	18.1	17.8	34.0	25.5	15.8	14.6
	3	1.3	1.7	5.8	7.0	18.1	21.7	6.1	7.5

Numbers are percentages
* p=0.005 (Overall Chi-Square test).

Women had more severe periventricular (OR 1.2; 95% CI 0.9-1.7) and subcortical white matter lesions (OR 1.1; 95% CI 0.8-1.5) than men, especially in the frontal region (OR 1.6; 95% CI 1.2-2.1 and OR 1.6; 95% CI 1.2-2.2, for severe frontal periventricular and subcortical white matter lesions, respectively).

Discussion

Our study shows that the severity of subcortical and periventricular white matter lesions is dependent on age and sex. We confirmed the significant association between severity of white matter lesions and age. In addition we showed that women more often had white matter lesions of both kinds, especially in the frontal region.

The strength of this study is its large number of elderly people, including institutionalized persons. Another important feature of our study is the distinction between white matter lesions in the subcortical and the periventricular region, and according to lobe.

However, some potential methodological shortcomings need to be considered. Our study had a response rate of 73 percent in subjects aged 60-70 years decreasing to 48 percent in participants aged between 80-90 years. This may lead to selection bias, especially in the oldest age category. We consider it likely that if participation in our study were related to the degree of white matter lesions, this would probably have resulted in persons with more severe white matter lesions participating less. Therefore the mean volume of subcortical white matter lesions and the mean grade of periventricular white matter lesions had probably been underestimated. This particularly applies to the oldest participants, among which the response was lowest. However, we consider it unlikely that the sex difference for white matter lesions has been influenced by of selection bias, since the response rate was similar for men and women in any age category.

Another point of concern is the validity of the white matter lesions rating scale, since there is potential for measurement error in this procedure. Although we chose anatomical landmarks to separate the lobes we cannot exclude that some misclassification occurred. As it is unlikely that this misclassification would be different for the sexes or age categories, and the resulting bias will be non-differential. When subcortical and periventricular white matter lesions are both abundantly present, it may sometimes be difficult to distinguish between the two. However, our intra -and inter-rater studies showed an excellent to high reliability, suggesting that this was not a major problem in our study.

An important aspect of our rating scale is that it distinguishes between subcortical and periventricular white matter lesions while also their severity was recorded. This will allow us to evaluate whether white matter lesions in these two regions have a different pathogenetic background and different clinical correlates.

Our study showed that subcortical white matter lesion volume was highest in the frontal and parietal lobes, a factor twenty and hundred higher than in the occipital and temporal lobes, respectively. Although the frontal and parietal lobes are larger than the occipital and the temporal lobe, this difference can not explain the vast difference in white matter lesion volume. Scheltens et al. found in a study of 24 'normal' elderly subjects (mean age 68.0 years) that the severity of white matter lesions was highest in the frontal lobe.[18] This observation was even more marked in subjects suffering from Alzheimer's disease. They explained this finding by overrepresentation of the frontal and parietal lobe compared with the occipital and the temporal lobes axial slices.[18] We cannot exclude that we have relatively overestimated the frontal or parietal lobes, but again the magnitude of the difference in the volume of white matter lesions seems out of proportion to this.

Our study confirms previous findings of a relatively high prevalence and severity of white matter lesions among women. This was also found in the Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study.[2,3] This could be mainly attributed to the significant differences for the subcortical and periventricular white matter lesions in the frontal region. It is unclear how these sex differences must be explained. One possibility is an increased susceptibility for ischemia of the brain secondary to the reduction in estrogen levels after menopause plays a role. The occurrence of hypoxia or ischemia in the cerebral white matter is commonly considered as an intermediate factor in the pathogenesis of white matter lesions.[6] Estrogens have important functions in the brain, including an increase in cerebral blood flow, protection against oxidative stress, stimulation of synaptogenesis and prevention of neuronal atrophy.[19-21] The post-menopausal estrogen reduction might make the female brain more vulnerable by reduction of cerebral blood flow (ischemia) and impairment of neuronal repair mechanisms. This hypothesis is supported by *in vitro* studies that showed protective effects of estrogens on menopause-related cerebral damage by excitotoxicity and the action of free radicals, as occurs during cerebral ischemia.[22-26] As there is a morphological and epidemiological overlap between vascular dementia and Alzheimer's disease, the increased prevalence of cerebral white matter lesions in women could underlie the higher incidence of Alzheimer's disease among women, even after adjustment for prolonged life expectancy, espe-

cially at high ages.[27] This hypothesis about the possible role of estrogens is supported by the finding of a significantly increased incidence of Alzheimer's disease among women who did not use estrogen replacement therapy.[28,29]

In conclusion, prevalence of cerebral white matter lesions increased with age. Women more often had severe white matter lesions compared to men. Large prospective population based studies are needed to investigate what underlies these differences and in particular to investigate whether estrogens play a part in the presence and development of white matter lesions and the attendant cognitive decline.

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Chapter 3

Blood pressure and cerebral white matter lesions

3.1 A follow-up study of blood pressure and cerebral white matter lesions

Abstract

White matter lesions are often observed on cerebral MRI-scans of elderly people. They are thought to play an important role in the pathogenesis of dementia. Cross-sectional studies have shown an association between elevated blood pressure and white matter lesions. We prospectively studied the relation between blood pressure level and changes with white matter lesions. In 1995-1996 we randomly sampled 1084 subjects aged between 60-90 years from two prospective population-based studies. One study had its baseline blood pressure measurement 20 years before, the other 5 years before. All subjects underwent 1.5T MRI-scanning and white matter lesions in the subcortical and periventricular regions were rated separately. The level of diastolic blood pressure assessed 20 years ago was significantly associated with subcortical and periventricular white matter lesions (RR 1.3; 95% CI 1.0-1.7 and RR 1.2; 95% CI 1.0-1.6 per 10 mm Hg, respectively). These associations were similar for systolic blood pressure. We found a J-shaped association between a 20-year change in diastolic blood pressure and subcortical white matter lesions (RR 2.2; 95% CI 1.0-5.2 and RR 3.2 95%; CI 1.4-7.4 for a decrease or an increase over 10 mm Hg, respectively). There was a linear association between the concurrent level of diastolic blood pressure and white matter lesions in subjects without a history of myocardial infarction, while this association was J-shaped in subjects with a

history of myocardial infarction. This study suggests a J-shaped relation between a long-term change in diastolic blood pressure, current diastolic blood pressure level and white matter lesions in a high risk group. Our results indicate that the J-shape relationship of diastolic blood pressure is not restricted to cardiovascular disease, but is also manifest in cerebrovascular disease.

Introduction

Cerebral white matter lesions are frequently observed on magnetic resonance imaging (MRI) scans of elderly, non-demented persons.[1-3] There is growing evidence that these white matter lesions play an important role in the development of cognitive decline and dementia.[3-6] Population-based MRI studies have shown a linear association between both diastolic and systolic blood pressure level and severity of cerebral white matter lesions.[1-3] However, this relation has been studied only cross-sectionally or in studies with a short follow up,[2] whereas blood pressure is known to change during aging, possibly in part due to atherosclerosis.[7,8] Witteman et al. have shown that the relation between a change in diastolic blood pressure and progression of atherosclerosis is J-shaped.[8] In accordance with that observation, other studies among elderly subjects suggested that both a low and high diastolic blood pressure are associated with increased risk of cardiovascular disease, in particular among subjects with preexisting heart disease.[9-12] There is conflicting evidence whether this J-curve applies to the relation between blood pressure and cerebrovascular disease,[13-15] and it is not known how white matter lesions are related to blood pressure changes over time.

We studied the presence of white matter lesions in relation to blood pressure level and change over a long period (20 years) and a short period (5 years) in a longitudinal population-based study. In addition, we investigated the association of white matter lesions with level of concurrent blood pressure, and also with change of blood pressure levels assessed 5 and 20 years before, among subjects with and without a history of myocardial infarction.

Subjects and Methods

Study Population

The Rotterdam Scan Study was designed to study determinants and consequences of brain abnormalities in the elderly. In 1995-1996, 1904 sub-

jects aged between 60-90 years were randomly selected in strata of age (5 years) and sex from two large ongoing prospective follow-up cohort studies, the Zoetermeer Study and the Rotterdam Study. The Zoetermeer Study had its baseline data-collection from 1975-1978; the mean follow up period was 19.6 years. The Rotterdam Study had the baseline data collection from 1990-1993; mean follow up period was 4.8 years. Both studies have been described in detail elsewhere.[16,17] In brief, the Zoetermeer Study is a prospective population-based study among 10361 subjects, aged between 5-91 years at baseline, of determinants of various chronic diseases. The Rotterdam Study is a population-based prospective cohort study, among 7983 elderly subjects aged 55 years and over, of determinants of neurological, cardiovascular, locomotor and ophthalmologic diseases in the elderly.

For the follow-up examination in the Rotterdam Scan Study subjects were invited by letter, and subsequently contacted by telephone. Upon agreement to participate in the study a list of contraindications was reviewed in order to assess eligibility (non eligible were those with dementia or blindness; or presence of MRI contraindications, including prosthetic valves, pacemaker, cerebral aneurysm clips, a history of intra ocular metal fragment, cochlear implants and claustrophobia). Of the baseline Zoetermeer Study and the Rotterdam Study cohorts 22% and 24% of the eligible population for the Rotterdam Scan Study, had died before follow-up. From 1904 invited subjects 1724 were eligible. Complete information, including a cerebral MRI scan, was obtained from 1084 persons (response 63%); 568 were from the Rotterdam Study (response 68%) and 516 from the Zoetermeer Study (response 58%). The response rate declined from 73% among subjects aged between 60-70 years to 48% among participants aged between 80-90 years in 1995-1996. Each participant signed an informed consent form. The study was approved by the medical ethics committee of Erasmus University.

Measurement of Risk Factors

Physical examinations and questionnaires were administered in a similar way both at baseline and follow up in the two sub-populations of the Rotterdam Scan Study. Blood pressure level was measured twice on the right arm in sitting position, by means of a random zero sphygmomanometer. The average of these measurements was used. Hypertension was defined as a systolic blood pressure $\geq$ 160 mm Hg and/or a diastolic blood pressure $\geq$ 95 mm Hg and/or self reported use of blood pressure lowering drugs. Height and weight were measured without shoes in light clothing. The body mass index was calculated as weight divided by height square.

Information on smoking behavior was obtained through standardized questionnaires, which were checked by a physician during an interview. Serum total cholesterol was measured at baseline using an automated enzymatic method.[18] Diabetes mellitus was considered present at baseline if the participant was taking oral anti-diabetics or insulin (in both subpopulations), and in addition if the random or post-load glucose level was higher than 11.1 mmol/l (in subjects originating from the Rotterdam Study).[19] A 12 lead ECG was recorded and stored digitally during baseline data-collection of the Rotterdam Study (n=555) and at follow-up (n=960). ECGs were missing mostly due to technical reasons (disturbances in power supply or technical problems with the recorder). All ECGs were analyzed by the Modular ECG Analysis System (MEANS).[20,21] For myocardial infarction the MEANS diagnosis was used.

MRI Scanning Protocol

An axial T1, T2 and Proton Density (PD) weighted cerebral MRI scan was made on a 1.5T MRI scan in all participants. Subjects recruited from the Zoetermeer Study were scanned with a 1.5T MR Gyroscan (Philips, Best, The Netherlands) and participants from the Rotterdam Study were scanned with a 1.5T MR VISION (Siemens, Erlangen, Germany). In order to achieve comparability the following pulse sequences were applied: at the Gyroscan T1 (TR 485 ms, TE 14 ms), T2 (TR 2236 ms, TE 90 ms) and PD (TR 2236 ms, TE 20 ms); and at the VISION: T1 (TR 700 ms, TE 14 ms), T2 (TR 2200 ms, TE 80 ms) and PD (TR 2200 ms, TE 20 ms). Slice thickness was 6 mm and 5 mm respectively, with an inter-slice gap of 20.0%. The images were printed on hard copy with a reduction factor of 2.7.

White Matter Lesions Rating Scale

White matter lesions were considered present if these were hyper-intense on both PD and T2 weighted images and not hypo-intense on T1 weighted image. White matter lesions were distinguished into those in the subcortical and periventricular region. The number and size of subcortical white matter lesions were rated on hard copy according to their largest diameter in categories of small (<3 mm), medium (3-10 mm) or large lesions (>10 mm). In order to calculate the volume of subcortical white matter lesions on hard copy, they were considered to be spherical with a fixed diameter per size category. Periventricular white matter lesions were rated semi-quantitatively per region: adjacent to the frontal horn (frontal capping), adjacent to the lateral wall of the lateral ventricles (bands) and adjacent to the occipital horn (occipital capping), on a scale including 0 (no white

matter lesions), 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 three regions (range 0-9). All MRI scans were examined by two raters from a pool of four experienced raters. In case of disagreement of more than one point, a consensus reading was held; in all other cases the readings of both readers were averaged. The inter- and intra-rater studies showed a good to excellent agreement. Weighted kappas for grading the periventricular white matter were between 0.79-0.90. For total subcortical white matter volume the inter- and intra-rater intra-class correlation coefficients were 0.88 and 0.95, respectively.

Statistical Analysis

We calculated relative risks (RR), as estimated by the odds ratio, by means of age and sex adjusted logistic regression to quantify the association between blood pressure and presence of severe white matter lesions. White matter lesions were dichotomized at the upper quintile. Additional adjustments were made for possible baseline confounding factors, including body mass index (kg/m^2), serum total cholesterol level (mmol/l), smoking behavior (never, former, current) and diabetes mellitus (absent/present).

The association between baseline blood pressure level and presence of white matter lesions was assessed both in quartiles of the blood pressure distribution and with blood pressure as a continuous variable in the multivariate model. Since this relation proved to be linear, we only present the results of the continuous analysis. We also investigated the presence of white matter lesions as a function of long-term change in blood pressure among subjects from the Zoetermeer Study and as a function of short-term change in blood pressure among subjects from the Rotterdam Study. Changes in blood pressure were grouped in four categories in order to distinguish between subjects with a decrease or an increase in blood pressure. For a change in diastolic blood pressure these categories were < -10 mm Hg, -10-0 mm Hg, 0-10 mm Hg and ≥ 10 mm Hg, whereas for systolic blood pressure these categories were < 0 mm Hg, 0-20 mm Hg, 20-40 mm Hg and ≥ 40 mm Hg. The second category was used as the reference for change in both diastolic and systolic blood pressure upon data inspection.

It has been suggested that a J-shaped association between diastolic blood pressure level and cardiovascular risk is mainly restricted to subjects with preexisting symptomatic coronary heart disease.[9-12] We therefore investigated the relation between quartiles of concurrent diastolic

blood pressure level and white matter lesions among subjects with (n=99) and without (n=861) a history of myocardial infarction (identified during follow up). To show a possible J-shaped association in this analysis, the third quartile was used as the reference upon data inspection. The same analyses were performed for systolic blood pressure. We were not able to investigate the relation by category of change in blood pressure and white matter lesions in subjects with a history of myocardial infarction due to small numbers. All relative risks are presented with a 95% confidence interval (95% CI).

Results

Table 1 presents both baseline and follow up characteristics of the study population. Mean age of the participants was 72.3 years (SD 7.4) at follow up, 52% of then was female. The mean systolic and diastolic blood pressure at follow-up was 147.3 mm Hg (SD 21.6) and 78.7 mm Hg (SD 11.7), respectively. Of all participants 51.3% had hypertension at follow-up.

Table 1
Characteristics of the Total Study Population in 1995/1996 (Follow-up, at MRI ascertainment) and the Baseline characteristics of the Long-Term (Baseline 1975-1978) and Short-Term (Baseline 1990-1993) Part of the Study Population.*

Characteristic	Baseline 1975-1978	Baseline 1990-1993	Follow up (1995-1996)
Number of subjects	516	568	1084
Number according to age at follow up			
60-70 years	253	213	466
70-80 years	213	205	418
80-90 years	50	150	200
Mean age (years)	51.2 (6.6)	69.0 (8.0)	72.3 (7.4)
Women (%)	53.3	51.1	52.0
Body Mass Index (kg/m^2)	25.0 (3.0)	26.3 (3.4)	26.6 (4.0)
Systolic BP (mm Hg)	131.5 (17.1)	136.8 (20.4)	147.3 (21.6)
Diastolic BP (mm Hg)	81.4 (10.8)	73.2 (10.9)	78.7 (11.7)
Serum cholesterol (mmol/l))	6.1 (1.1)	6.7 (1.2)	not determined
Hypertension (%)	25.2	39.2	51.3
Diabetes Mellitus (%)	1.0	6.9	6.9
Smokers (%)			
current	36.7	20.0	17.7
former	34.4	45.5	44.7
never	28.8	34.5	37.6

* Values are unadjusted means (standard deviation) or percentages.

Table 2
The Relative Risk of Baseline Blood Pressure for Presence of Cerebral White Matter Lesions.*

	age at MRI	Relative risk of white matter lesions per 10 mm Hg increase in blood pressure (95% confidence interval)†			
		diastolic blood pressure		systolic blood pressure	
		baseline (1975-1978)	baseline (1990-1993)	baseline (1975-1978)	baseline (1990-1993)
Subcortical white matter lesions	60-70	1.5 (1.0-2.3)	1.6 (1.1-2.4)	1.2 (0.9-1.6)	1.1 (0.9-1.4)
	70-80	1.3 (0.9-1.9)	1.2 (0.9-1.6)	1.2 (0.9-1.4)	1.1 (0.9-1.2)
	80-90	1.1 (0.6-2.2)	1.9 (1.3-2.7)	1.1 (0.8-1.6)	1.0 (0.9-1.1)
	overall	1.3 (1.0-1.7)	1.5 (1.2-1.8)	1.1 (1.0-1.3)	1.1 (1.0-1.2)
Periventricular white matter lesions	60-70	1.9 (1.2-3.1)	1.5 (0.9-2.2)	1.5 (1.1-2.1)	1.1 (0.9-1.1)
	70-80	1.2 (0.9-1.6)	1.1 (0.8-1.5)	1.1 (0.9-1.3)	1.0 (0.9-1.2)
	80-90	0.8 (0.5-1.5)	1.4 (1.0-1.9)	1.0 (0.7-1.3)	0.9 (0.8-1.1)
	overall	1.2 (1.0-1.6)	1.3 (1.1-1.6)	1.1 (1.0-1.3)	1.0 (0.9-1.1)

* dichotomized at the upper quintile of the severity distribution of white matter lesions.
† age and sex adjusted.

Non-responders from the original Zoetermeer Study and the original Rotterdam Study differed significantly from responders with respect to age (75.6 versus 70.8 years; p <0.001 and 76.6 versus 73.7 years; p <0.01 respectively), but not with respect to sex, diastolic blood pressure and the prevalence of hypertension at baseline. Non-responders from the Zoetermeer Study, but not from the Rotterdam Study, had a higher systolic blood pressure (135.3 mm Hg versus 132.8 mm Hg, p=0.05) at baseline.

At follow-up, 20% and 8% of all participants were without any periventricular or subcortical white matter lesions, respectively. The median volume of subcortical white matter lesions on hard copy was 3.8 ml and the median grade of periventricular white matter lesions was 2 (on a scale from 0-9). Both median volume of subcortical white matter lesions and mean grade of periventricular white matter lesions increased significantly with age.

The presence of white matter lesions linearly increased with increasing baseline blood pressure level (table 2). The relative risks of concurrent diastolic blood pressure level for subcortical and periventricular white matter lesions were 1.4 (95% CI 1.2-1.6) and 1.2 (95% CI 1.1-1.4) per 10 mm Hg increase of blood pressure level, respectively. For concurrent systolic blood pressure level these relative risks were 1.2 (95% CI 1.1-1.2) and 1.1 (95% CI 1.0-1.2) per 10 mm Hg increase of blood pressure level, respectively. The associations were strongest in the youngest age group. Adjustment for other confounders, including smoking status, presence of diabetes and body mass index, did not alter the magnitude of the associations. The same was true when subjects using anti-hypertensive drugs were excluded from the analyses. When the analyses for concurrent blood pressure levels were performed in the Rotterdam and Zoetermeer population separately, the associations were similar to those based on the entire Rotterdam Scan Study population.

Table 3 presents the relative risks of white matter lesions by blood pressure change over 20 years. Subjects with a decrease or an increase in diastolic blood pressure of more than 10 mm Hg had significantly more often periventricular or subcortical white matter lesions than the reference group. This J-shaped association was most marked for subcortical white matter lesions. The J-curve remained when subjects on anti-hypertensive drugs at baseline or follow up (n=166) were excluded from the analysis. For change in systolic blood pressure, subjects with an increase of 40 mm Hg or more, more often had both types of white matter lesions, while a decrease of systolic blood pressure was not significantly associated with either type of white matter lesions. The associations were strongest in the youngest subjects. The relative risks for subcortical white matter lesions for subjects aged between 60-70 years at MRI-scanning

Table 3
The Relative Risk of a Change in Blood Pressure over 20 Years for Presence of Severe White Matter Lesions* (RR with 95% CI).

Category (mm Hg)	Change in diastolic blood pressure			
	< -10 mm Hg (n=99)	-10-0 mm Hg (n=149)	0-10 mm Hg (n=150)	≥ 10 mm Hg (n=112)
Subcortical white matter lesions				
Adjusted for age and sex	2.2 (1.0-5.2)	1.0 (ref)	1.7 (0.8-4.0)	3.2 (1.4-7.2)
Adjusted for age, sex and cardiovascular risk factors†	2.3 (1.0-5.4)	1.0 (ref)	1.8 (0.8-4.1)	3.3 (1.4-7.5)
Periventricular white matter lesions				
Adjusted for age and sex	1.8 (0.9-3.5)	1.0 (ref)	1.0 (0.5-2.0)	1.6 (0.8-3.2)
Adjusted for age, sex and cardiovascular risk factors†	1.7 (0.8-3.4)	1.0 (ref)	1.0 (0.5-2.2)	1.8 (0.9-3.9)
Category (mm Hg)	Change in systolic blood pressure			
	< 0 mm Hg (n=94)	0-20 mm Hg (n=204)	20-40 mm Hg (n=138)	≥ 40 mm Hg (n=74)
Subcortical white matter lesions				
Adjusted for age and sex	1.2 (0.5-2.6)	1.0 (ref)	0.9 (0.4-1.9)	2.8 (1.4-5.8)
Adjusted for age, sex and cardiovascular risk factors†	1.3 (0.6-2.9)	1.0 (ref)	0.9 (0.4-2.0)	2.7 (1.3-5.6)
Periventricular white matter lesions				
Adjusted for age and sex	1.2 (0.6-2.6)	1.0 (ref)	0.8 (0.4-1.7)	1.9 (0.9-3.8)
Adjusted for age, sex and cardiovascular risk factors†	1.3 (0.6-2.7)	1.0 (ref)	1.0 (0.5-2.1)	2.1 (1.0-4.3)

* dichotomized at the upper quintile of the severity distribution of white matter lesions.
† cardiovascular risk factors: diabetes mellitus, smoking behaviour, serum cholesterol and long-term change in body mass index.
ref = reference group.

Table 4
The Relative Risk of a Change in Blood Pressure over 5 Years for Presence of Severe White Matter Lesions* (RR with 95% CI).

Category (mm Hg)	Change in diastolic blood pressure			
	< -10 mm Hg (n=58)	-10-0 mm Hg (n=144)	0-10 mm Hg (n=209)	≥ 10 mm Hg (n=156)
Subcortical white matter lesions				
Adjusted for age and sex	1.4 (0.7-3.0)	1.0 (ref)	1.7 (0.9-2.6)	1.0 (0.6-1.8)
Adjusted for age, sex and cardiovascular risk factors†	1.5 (0.7-3.4)	1.0 (ref)	1.5 (0.9-2.7)	0.8 (0.4-1.5)
Periventricular white matter lesions				
Adjusted for age and sex	1.1 (0.5-2.5)	1.0 (ref)	1.2 (0.7-2.1)	1.0 (0.6-1.9)
Adjusted for age, sex and cardiovascular risk factors†	1.2 (0.5-2.7)	1.0 (ref)	1.2 (0.7-2.2)	0.9 (0.5-1.7)
Category (mm Hg)	Change in systolic blood pressure			
	< 0 mm Hg (n=165)	0-20 mm Hg (n=233)	20-40 mm Hg (n=138)	≥ 40 mm Hg (n=31)
Subcortical white matter lesions				
Adjusted for age and sex	1.3 (0.7-2.5)	1.0 (ref)	1.5 (0.9-2.6)	2.1 (0.9-2.5)
Adjusted for age, sex and cardiovascular risk factors†	1.1 (0.7-1.9)	1.0 (ref)	1.3 (0.7-2.3)	1.9 (0.7-5.2)
Periventricular white matter lesions				
Adjusted for age and sex	1.3 (0.8-2.2)	1.0 (ref)	1.3 (0.8-2.2)	0.9 (0.3-2.6)
Adjusted for age, sex and cardiovascular risk factors†	1.3 (0.8-2.3)	1.0 (ref)	1.2 (0.7-2.2)	1.1 (0.3-3.3)

* dichotomized at the upper quintile of the severity distribution of white matter lesions.
† cardiovascular risk factors: diabetes mellitus, smoking behaviour, serum cholesterol and long-term change in body mass index.
ref = reference group.

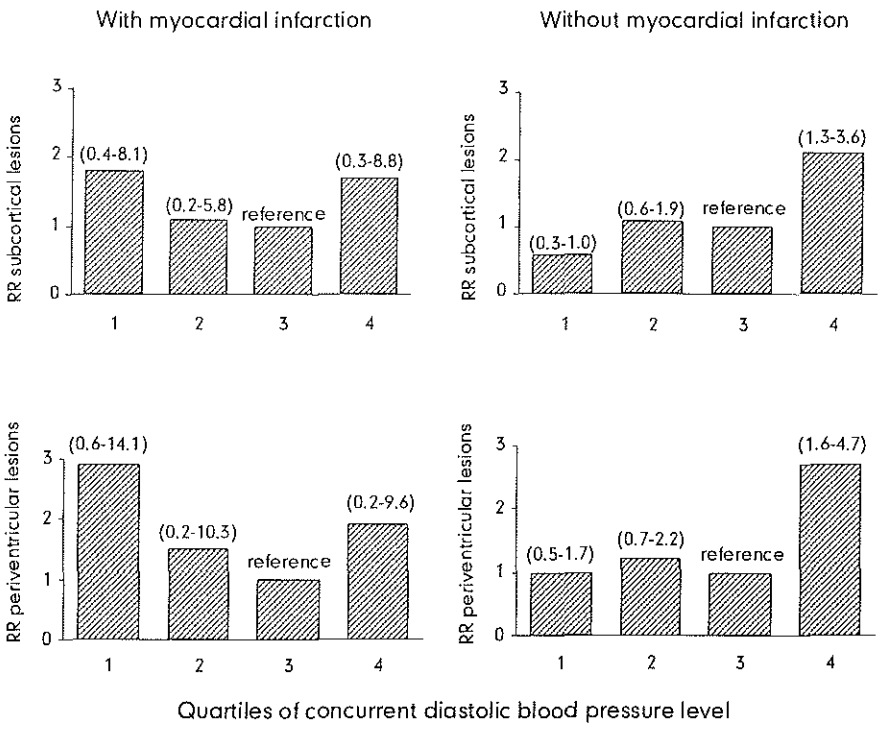

Figure 1
The association between concurrent diastolic blood pressure level (in quartiles) and white matter lesions in subjects with or without a history of myocardial infarction.

were 3.5 (95% CI 0.7-17.4) and 5.1 (95% CI 1.2-17.4) for a decrease or increase of more than 10 mm Hg in diastolic blood pressure, respectively (data not shown in table 3). Exclusion of subjects with a history of myocardial infarction virtually did not change the magnitude of the associations (not shown in table 3).

Table 4 shows the association between changes in blood pressure over 5 years and presence of white matter lesions. No clear association between a short-term change in diastolic or systolic blood pressure and white matter lesions was observed. This was irrespective of a history of myocardial infarction (not shown in table 4).

Figure 1 shows that the association between quartiles of concurrent diastolic blood pressure level and presence of white matter lesions in subjects with a history of myocardial infarction was J-shaped for both types of white matter lesions. If subjects on current anti-hypertensive treatment (n=46) were excluded from this group the J-curve became even more pronounced, though the confidence intervals became wider. We found no clear association with current systolic blood pressure level

among subjects with a history of myocardial infarction. In subjects without a history of myocardial infarction there was a linear association between current diastolic blood pressure level and white matter lesions (fig 1), and this relation was similar for systolic blood pressure.

Discussion

We studied the occurrence of cerebral white matter lesions in relation to baseline blood pressure and long-term and short-term changes in blood pressure in a prospective population-based study among elderly subjects. We found that levels of diastolic and systolic blood pressure were associated with the presence of both subcortical and periventricular cerebral white matter lesions. There was a J-shaped association between a change of diastolic blood pressure over a 20 years and presence of cerebral white matter lesions. In subjects with a history of myocardial infarction the association between current diastolic blood pressure level and both types of white matter lesions was J-shaped, while this relation was linear in other subjects.

The 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. However, some limitations and methodological issues need to be pointed out. The overall response rate was 63%, leading to potential selection bias, especially among the oldest participants. However, we consider it unlikely that selection bias has played a major role in our study since there were only small, mainly non-significant, differences with respect to baseline blood pressure and prevalence of hypertension between responders and non-responders. We cannot exclude that our relative risks are somewhat underestimated because we performed our study in survivors of the two baseline studies. Subjects who had died between baseline examination and follow up may have had a more severe decrease or increase in blood pressure compared to those who survived.

We found the strongest associations in the youngest age category. There are various explanations for this. One is selective survival among the oldest age category. Subjects now aged between 80-90 years were aged between 60-70 years 20 years ago. It seems plausible that only the healthiest subjects survived another 20 years and could again participate at follow up. Another explanation for the weak association at higher ages between blood pressure levels and white matter lesions might be that in

elderly subjects presence of a risk factor has less discriminative power and that many other risk factors for white matter lesions co-exist.

One should consider that the association between blood pressure and white matter lesions might be confounded by other vascular risk factors. However, adjustment for differences in cardiovascular risk factors did not significantly alter the observed associations between blood pressure and white matter lesions. This suggests that these associations can not or only partly be attributed to confounding by other cardiovascular risk factors, and that white matter lesions are independently related to, and perhaps a consequence of, elevated blood pressure levels, or of blood pressure changes.

The rationale of investigating the relation of white matter lesions as a function of a change of diastolic blood pressure is that change may be a better predictor of cardiovascular disease than the actual level of blood pressure, since the level is the resultant of a life-long exposure to factors that have influenced the blood pressure, but does not provide information on the previous blood pressure level.[8] We found a J-shaped relation between change of diastolic blood pressure over a period of 20 years on the one hand and subcortical and periventricular white matter lesions on the other. This J-curve could in part be attributed to the subjects with a history of a myocardial infarction. If those subjects were excluded from the analyses the J-shaped association persisted. This is in agreement with our finding of a J-shaped relation between concurrent diastolic blood pressure level and white matter lesions in subjects with a history of myocardial infarction and not in those without. A J-shaped association is a common finding in the relation between diastolic blood pressure level and cardiovascular disease and mortality, although its explanation is still a matter of debate.[9-12,22] Many studies have shown that the J-shaped relation between diastolic blood pressure level and cardiovascular disease is confined to subjects at high risk (especially those with a history of myocardial infarction or a diseased coronary circulation).[9-12] Our findings are in accordance with that observation. It has also been suggested that a too aggressive anti- hypertensive treatment, with lowering of blood pressure beyond a critical point, might contribute to this J-shape.[11] However, if we excluded subjects on blood pressure lowering drugs the J-shape remained.

A possible explanation for the J-shaped association might be that among persons with advanced vascular pathology, possibly on the basis of longstanding hypertension, cerebral autoregulation is impaired. Those persons are presumably the ones with a severe decrease in diastolic blood pressure[8] or with a history of myocardial infarction, whereas in healthy individuals during a reduction or increase of blood pressure the cerebral

blood flow is maintained via the mechanism of autoregulation.[23] As a result of the impaired autoregulation, the lower limit of blood pressure at which the autoregulation still functions properly shifts towards a higher blood pressure level,[23,24] so that even normotensive levels of blood pressure may result in hypo-perfusion of the white matter in these persons.[25] In subjects with an impaired autoregulation, a reduction of cerebral blood flow will primarily affect areas with an already marginal blood supply under physiological conditions, such as the subcortical and periventricular white matter.[26-28] This is in agreement with the finding of impaired autoregulation and a reduction of cerebral blood flow among subjects with periventricular white matter lesions.[29,30] In contrast, in people with a lifelong low diastolic blood pressure autoregulation is not impaired, and they therefore have a normal cerebral blood flow, even at a low blood pressure level. In our study those people were indeed at the lowest risk for white matter lesions.

This study suggests a J-shaped relation between a 20 year change in diastolic blood pressure, current diastolic blood pressure level and white matter lesions in a high risk group. Our results indicate that the J-shape relationship of diastolic blood pressure is not restricted to cardiovascular disease, but also applies to cerebrovascular disease. This may have important clinical implications for the treatment of hypertension in these high-risk group subjects. Further prospective studies are needed in order to unravel the causal chain of events between blood pressure changes, cerebral perfusion and emergence of white matter lesions.

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3.2 Duration and treatment of hypertension and cerebral white matter lesions

Abstract

Background *White matter lesions are frequently observed on cerebral magnetic resonance imaging scans of elderly people and are thought to play an important role in the pathogenesis of dementia. Hypertension has been associated with the presence of white matter lesions but this has almost exclusively been investigated in cross-sectional studies. We prospectively studied the association of these lesions with previous and current hypertension, and also its duration and treatment.*

Methods *We randomly sampled 1084 subjects aged between 60-90 years from two prospective population-based studies. One half of the study subjects had its baseline hypertension assessment in 1975-1978, the other in 1990-1993. All subjects underwent 1.5T MRI-scanning; white matter lesions in the subcortical and periventricular regions were rated separately.*

Results *Subjects with hypertension had an increased rate of both types of white matter lesions. Duration of hypertension was associated with both periventricular and subcortical white matter lesions. There was a strong effect modification by age in this relation. For participants aged between 60-70 years during follow-up, with over 20 years of hypertension, the relative risks for subcortical and periventricular white matter lesions were 21.8 (95% CI 4.6-103) and 16.1 (95% CI 3.4-77.3) respectively, compared with normotensive subjects. Subjects*

with current hypertension (controlled or uncontrolled) had a moderately increased rate of subcortical white matter lesions (RR 1.9; 95% CI 1.2-2.9 and RR 3.0; 95% CI 1.9-4.9, respectively) compared with normotensive subjects. For periventricular white matter lesions these associations were similar.

Conclusions *Our results suggest that the most unbiased risk estimates are from subjects aged 40-50 at baseline and 60-70 at follow-up. There is a dose dependent relation between duration of hypertension and white matter lesions. Effective treatment reduces the rate of both types of white matter lesions and may thus prevent or reduce the attendant cognitive impairment or dementia.*

Introduction

Cerebral white matter lesions are frequently observed on magnetic resonance imaging (MRI) scans of elderly, non-demented people.[1-3] There is growing evidence that these white matter lesions play an important role in the development of cognitive decline and dementia.[3-6] The pathogenesis of white matter lesions remains largely unknown, but it is generally considered that hypertension and other vascular risk factors are involved.[1-3,7,8] The relation between hypertension and white matter lesions has thus far been investigated mainly in cross-sectional studies of elderly subjects,[1,3] in one study with a relatively short follow-up of about 6 years,[2] and in a male cohort from the NHBLI twin study, with 25 years of follow up.[9] Results from one of the two longitudinal studies suggested that effective treatment of hypertension may reduce the risk for white matter lesions,[2] and recently the Syst-Eur investigators reported that in people with isolated systolic hypertension antihypertensive treatment significantly reduced the incidence of dementia.[10]

Hypertension in the elderly may have been present for a long period. If hypertension early in life would indeed be related to white matter lesions later in life, effective treatment of hypertension may prevent or delay the emergence of white matter lesions and of the attendant cognitive impairment.

We prospectively investigated the association between duration and treatment status of hypertension and the presence of cerebral white matter lesions.

Methods

Study Population

The Rotterdam Scan Study was designed to study determinants and consequences of age related brain abnormalities in the elderly. In 1995-1996, 1904 subjects aged between 60-90 years were randomly selected in strata of age (5 years) and sex from two large ongoing prospective follow-up cohort studies, the Zoetermeer Study and the Rotterdam Study. The Zoetermeer Study had its baseline data collection from 1975-1978; the mean follow-up period was 19.6 years. The Rotterdam Study had the baseline data-collection from 1990-1993; mean follow-up period was 4.8 years. Both studies have been described in detail elsewhere.[11,12] In short, the Zoetermeer Study is a prospective population-based study among 10361 subjects, aged between 5-91 years at baseline; the study originally addressed determinants of chronic diseases. The Rotterdam Study is a population-based prospective cohort study, among 7983 elderly subjects aged 55 years and over, which studies determinants of neurological, cardiovascular, locomotor and ophthalmologic diseases in the elderly.

For the follow-up examination in the Rotterdam Scan Study subjects were invited by a letter, and were subsequently contacted by telephone. Upon agreement to participate in the study a list of contraindications was reviewed in order to assess eligibility (dementia; blindness; or presence of MRI contraindications, including prosthetic valves, pacemaker, cerebral aneurysm clips, a history of intra-ocular metal fragments, cochlear implants or claustrophobia). From 1904 invited subjects 1724 were eligible. Complete information was obtained, including a cerebral MRI scan, from 1084 persons (response 63%); 568 from the Rotterdam Study (response 68%) and 516 from the Zoetermeer Study (response 58%). The response rate declined from 73% among subjects aged between 60-70 years to 48% among participants aged between 80-90 years (in 1995-1996). Each participant signed an informed consent from. The study was approved by the medical ethics committee of the Erasmus University.

Measurement of risk factors

Physical examinations and standardized questionnaires were administered in a similar way both at baseline and at follow-up in the two subpopulations of the Rotterdam Scan Study. At baseline and follow-up, blood pressure was measured two times on the right arm with a random zero sphygmomanometer in sitting position. The average of these measurements of systolic blood pressure and diastolic blood pressure was

used. Hypertension was defined as a diastolic blood pressure ≥ 95 mm Hg and/or a systolic blood pressure ≥ 160 mm Hg and/or the self reported use of blood pressure lowering medication. Information on blood pressure lowering medication was assessed by means of a computerized, structured questionnaire, which was checked by a physician.

Height and weight were measured in light clothing. The body mass index was calculated as weight divided by height square. Information on smoking behavior was obtained with the use of a standardized questionnaire, which was checked by a physician during the interview. Diabetes mellitus was considered present if the participant was taking oral anti diabetics or insulin (both sub-populations) or if the random or post load glucose level was higher than 11.1 mmol/l (subjects originating from the Rotterdam Study).[13]

MRI Scanning protocol

From all participants an axial T1, T2 and Proton Density (PD) weighted cerebral MRI scan was made on a 1.5T MRI scan. Subjects recruited from the Zoetermeer Study were scanned with a 1.5T MR Gyroscan (Philips, Best, The Netherlands) and participants from the Rotterdam Study were scanned with a 1.5T MR VISION (Siemens, Erlangen, Germany). In order to provide comparability the following pulse sequences were applied: at the Gyroscan T1 (TR 485 ms, TE 14 ms), T2 (TR 2236, TE 90 ms) and PD (TR 2236 ms, TE 20 ms); and at the VISION: T1 (TR 700 ms, TE 14 ms), T2 (TR 2200 ms, TE 80 ms) and PD (TR 2200 ms, TE 20 ms). Slice thickness was 6 mm and 5 mm respectively, with an inter-slice gap of 20.0%. The images were printed on hard copy with a reduction factor of 2.7.

White Matter Lesions Rating Scale

White matter lesions were considered present if these were hyper-intense on both PD and T2 weighted images and not hypo-intense on T1 weighted images. White matter lesions were distinguished into those in the subcortical and periventricular regions. The number and size of subcortical white matter lesions was rated on hard copy according to their largest diameter in categories of small (<3 mm), medium (3-10 mm) or large lesions (>10 mm). In order to calculate the volume of subcortical white matter lesions on hard copy, they were considered to be spherical with a fixed diameter per size category. Periventricular white matter lesions were rated semi-quantitatively per region: adjacent to frontal horns (frontal capping); adjacent to lateral wall of lateral ventricles (bands), and adjacent to occipital horns (occipital capping), on a scale ranging from 0 (no white matter lesions), 1 (pencil-thin periventricular lining), 2 (smooth halo

or thick lining) to 3 (large confluent white matter lesions). The overall degree of periventricular white matter lesions was calculated by adding up the scores for the three separate categories (range 0-9). All MRI scans were examined by two raters from a pool of four experienced raters. In case of disagreement by more than one point, a consensus reading was held; in all other cases the readings of both readers were averaged. The inter- and intra-rater studies showed a good to excellent agreement. Weighted kappas for grading the periventricular white matter were between 0.79-0.90. For total subcortical white matter volume the inter- and intra-rater intra-class correlation coefficient was 0.88 and 0.95, respectively.

Statistical Analysis

The relation between hypertension, its duration and treatment, and white matter lesions was assessed by age and sex adjusted logistic regression with the presence of severe white matter lesions as the dependent variable. The strength of the association was expressed as the relative risk (RR), as estimated by the odds ratio, and is presented with 95% confidence intervals (95% CI). White matter lesions were dichotomized at the upper quintile. Subjects without severe white matter lesions were the reference group (lower four quintiles). Additional adjustments were made for possible confounding factors, including body mass index, smoking behavior (never, former, current) and diabetes mellitus.

Duration of hypertension was studied in each of the two sub-populations separately, by putting dummy variables into the model for duration of hypertension. In participants originating from the Rotterdam Study duration could be estimated as less than 5 years (hypertension present in 1995/1996 but not in 1990-1993), or over 5 years (hypertension present in 1990-1993 and in 1995/1996). Whereas in participants originating from the Zoetermeer Study duration could be estimated as less than 20 years (hypertension present in 1995/1996 but not in 1975-1978); or over 20 years (hypertension present in 1975-1978 and in 1995/1996). Subjects without hypertension at baseline and at follow-up were the reference group. Subjects who were hypertensive at baseline (1990-1993 or 1975-1978), but no longer during the 1995-1996 data collection were excluded from the analysis (n=27 and n=23, respectively).

The relation between duration of hypertension and the presence of white matter lesions may be biased by selective survival, since hypertension is related to mortality.[14] Increased mortality might particularly occur with longstanding hypertension and among elderly subjects. We addressed this topic by age stratified analysis because we expected a smaller

effect of selective mortality in the youngest age category. In addition we compared the baseline prevalence of hypertension between survivors and those who died before the follow up assessment by means of age and sex adjusted analysis of covariance (ANCOVA).

The association between treatment status and white matter lesions was studied cross-sectionally by the introduction of dummy variables for treatment into the model. Participants who were identified as hypertensive during the data-collection of the Rotterdam Scan Study (1995-1996) were defined as treated if they reported the use of blood pressure lowering medication. Otherwise they were classified as untreated. Subjects were considered as treated and controlled if their systolic blood pressure was below 160 mm Hg and their diastolic blood pressure below 95 mm Hg. If their blood pressure still fulfilled criteria of hypertension they were classified as uncontrolled. Subjects without hypertension in 1995-1996 served as the reference group. In addition we separately estimated the duration of hypertension for the two sub-populations of the Rotterdam Scan Study (according to the previous criteria) by treatment status, in order to find out whether the association between treatment status and white matter lesions was confounded by duration (severity) of hypertension.

Results

Table 1 presents baseline and follow-up characteristics of both participants and non-participants of the two sub-populations of the Rotterdam Scan Study. The number of 60-70, 70-80 and 80-90 year old subjects were 213, 205 and 150 for those originating from the Rotterdam Study and 253, 213 and 50 subjects for those of the Zoetermeer Study, respectively. Of all subjects 20% had no periventricular white matter lesions, whereas 8% of all subjects was completely free of subcortical white matter lesions. Median volume of subcortical white matter lesions on hard copy was 3.9 ml. and the median grade of periventricular white matter lesions was 2 (range 0-9).

In both sub-populations non-participants were significantly older. Non-participants from the Zoetermeer Study had a significantly higher systolic blood pressure than participants did (137.2 mm Hg versus 131.4 mm Hg, $p<0.05$). The proportion with hypertension was approximately 25% larger in participants than in non-participants in both sub-populations, but the difference was not statistically significant.

Cumulative mortality among eligible subjects from the Zoetermeer sub-population in the age groups 40-50 years, 50-60 years and 60-70 years at baseline (1975-1978) was 8%, 17% and 47% respectively. For

Table 1
Characteristics of the baseline and follow-up (1995/1996, MRI ascertainment), in the Zoetermeer Study Study part (baseline1975-1978) and in the Rotterdam Study part (baseline 1990-1993) of the Rotterdam Scan Study.*

	Zoetermeer Study			Rotterdam Study		
	Baseline		Follow-up	Baseline		Follow-up
	Participants (n=516)	Non-participants (n=269)		Participants (n=568)	Non-participants (n=371)	
Mean age (years)	51.2 (6.6)	56.1 (7.1)†	70.8 (6.5)	69. 1 (8.0)	72.0 (8.0)†	73.6 (8.0)
Women (%)	53.2	59.7	53.5	50.3	58.5	50.0
Systolic BP (mm Hg)	131.4 (17.1)	137.2 (18.0)‡	148.8 (22.7)	136.8 (20.4)	139.3 (20.2)	146.1 (20.4)
Diastolic BP (mm Hg)	81.3 (10.9)	83.0 (11.5)	81.0 (11.6)	73.2 (10.9)	71.3 (10.9)	76.6 (11.4)
Body Mass Index (kg/m^2)	25.0 (3.0)	25.3 (3.1)	27.0 (3.7)	26.3 (3.4)	26.3 (3.4)	26.3 (3.5)
Hypertension (%)	25.5	31.4	51.2	39.2	48.6	51.6
Diabetes mellitus (%)	1.0	0.2	8.2	6.7	11.9	7.5
Smokers (%)						
current	37.1	38.3	15.9	19.4	18.8	19.4
former	34.6	25.1	55.3	45.0	38.4	45.7
never	28.3	36.6‡	28.8	35.6	42.7	34.9

*Values are unadjusted means (SD) or percentages.
† P<0.001 (age and sex adjusted ANCOVA or Chi-Square test when applicable).
‡ P<0.05 (age and sex adjusted ANCOVA or Chi-Square test when applicable).

eligible subjects from the Rotterdam sub-population, who were aged between 55-65 years, 65-75 years and 75-85 years at baseline (1990-1993), cumulative mortality for the relevant age category until follow up was 10%, 28% and 62% respectively.

In the Zoetermeer Study the difference in the prevalence of hypertension between those who had died before follow-up and those eligible was not significant in the youngest age category, and borderline significant in the 70-80 years and 80-90 years age category. In participants from the Rotterdam Study prevalence of hypertension in those who had died before follow-up was significantly higher than in those eligible for the youngest and middle age category, but not in the 80-90 years category (table 2).

Table 3 presents the association between duration of hypertension and presence of white matter lesions per age stratum. For participants aged between 60-70 years at follow-up, with over 20 years of hypertension, the relative risks for subcortical and periventricular white matter lesions were 21.8 (95% CI 4.6-103.2) and 16.1 (3.4-77.3) respectively, compared with non-hypertensives. There was a dose-response relation between the duration of hypertension and presence of either type of white matter lesions. A marked effect modification by age was observed.

Table 4 shows the cross-sectional association between treatment status and presence of cerebral white matter lesions. Since these associations were similar in both sub-populations they are presented for the study population as a whole. Subjects who had hypertension despite the use of blood pressure lowering drugs had the highest relative risk of having both types of white matter lesions, followed by the treated but con-

Table 2
Baseline prevalence of hypertension in eligible subjects compared with those who had died before follow-up, in the Zoetermeer Study part (baseline 1975-1978) and in the Rotterdam Study part (baseline 1990-1993) of the Rotterdam Scan Study.*

Age at follow-up (years)	Hypertension (%)					
	Zoetermeer Study			Rotterdam Study		
	Eligible	Dead at follow-up	*p*-value†	Eligible	Dead at follow-up	*p*-value†
60-70	20.0	26.6	*0.63*	28.2	56.0	*0.0003*
70-80	29.8	43.9	*0.06*	41.7	59.8	*0.001*
80-90	36.7	52.7	*0.06*	56.9	58.8	*0.67*
overall	27.9	37.8	*0.03*	44.2	55.1	*0.0006*

* Values are age and sex adjusted percentages.
† P-value by means of ANCOVA.

Table 3
The relation between duration of hypertension and presence of severe cerebral white matter lesions (RR and 95%CI).*

White matter lesions†	Age category	Duration of hypertension‡					
		Zoetermeer Study			Rotterdam Study		
		No hypertension§ (n=228)	< 20 years (n=155)	> 20 years (n=107)	No hypertension§ (n=241)	< 5 years (n=97)	> 5 years (n=191)
Subcortical	60-70	1.0	6.0 (1.5-24.5)	21.8 (4.6-103)	1.0	3.6 (1.1-11.4)	1.5 (0.5-4.8)
	70-80	1.0	2.4 (0.9-6.4)	1.3 (0.4-3.9)	1.0	0.9 (0.3-2.6)	2.5 (1.1-5.9)
	80-90	1.0	1.0 (0.2-5.7)	0.3 (0.0-2.3)	1.0	1.7 (0.5-5.2)	1.2 (0.5-2.6)
	overall	1.0	2.5 (1.3-4.9)	2.2 (1.0-4.7)	1.0	1.7 (1.0-3.2)	1.9 (1.1-3.1)
Periventricular	60-70	1.0	2.0 (0.5-8.9)	16.1 (3.4-77.3)	1.0	3.3 (0.9-11.4)	1.9 (0.5-6.8)
	70-80	1.0	0.7 (0.3-1.7)	1.3 (0.6-2.8)	1.0	1.2 (0.4-3.6)	2.4 (1.0-6.0)
	80-90	1.0	0.8 (0.2-4.0)	0.2 (0.0-1.1)	1.0	1.0 (0.3-2.9)	1.1 (0.5-2.5)
	overall	1.0	1.0 (0.5-1.8)	1.6 (0.8-3.0)	1.0	1.5 (0.8-2.8)	1.7 (1.0-2.8)

* Adjusted for age, sex, diabetes mellitus, body mass index, smoking behavior.
† Represents the upper quintile of the white matter lesions severity distribution.
‡ Hypertension: systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 95 and/or the use of blood pressure lowering drugs.
§ Reference group (subjects without hypertension neither at baseline nor at follow up).

trolled and the untreated hypertensives. Again, the association between treatment status and white matter lesions was most marked within subjects aged between 60 and 70 years.

Participants without hypertension had a mean systolic and diastolic blood pressure of 136.4 mm Hg (SD 14.0) and 74.7 (SD 9.8) respectively. These values were similar to those in participants with treated and controlled hypertension (mean systolic blood pressure 137.0 (SD 13.8); mean diastolic blood pressure 74.0 (SD 9.6). In contrast, for participants with treated uncontrolled and untreated hypertension these levels were 173.5 (SD 13.9) and 170.1 (SD 13.7) for systolic blood pressure and for diastolic blood pressure 88.0 (SD 9.7) and 88.4 (SD 9.6), respectively. There was no effect modification by age for these differences between the treated and untreated groups.

In the Rotterdam Study most of the untreated hypertensives (75%) had hypertension for less than 5 years, whereas this was the case for only 25% of both treated groups. In the Zoetermeer study 66% of the untreated hypertensives had hypertension for less than 20 years, whereas this was about 52% for both treated groups.

Table 4
The cross-sectional relation between hypertension, treatment status and the presence of severe cerebral white matter lesions (RR and 95% CI).*

White matter lesions†	Age (years)	Hypertension (all)	Hypertension treatment status‡		
			Untreated (n=189)	Treated, controlled (n=134)	Treated, uncontrolled (n=220)
Subcortical	60-70	4.5 (2.2-9.6)	4.2 (1.7-10.4)	3.4 (1.3-8.6)	8.5 (3.1-22.7)
	70-80	1.7 (1.0-2.8)	1.5 (0.7-2.9)	1.6 (0.8-3.1)	2.1 (1.0-4.4)
	80-90	1.5 (0.8-2.9)	1.2 (0.5-2.9)	1.3 (0.6-2.9)	2.0 (0.8-4.9)
	overall	2.2 (1.5-3.1)	1.9 (1.2-2.9)	1.9 (1.2-2.9)	3.0 (1.9-4.9)
Periventricular	60-70	2.7 (1.3-5.8)	1.9 (0.7-5.4)	2.4 (0.9-6.3)	5.4 (2.0-14.8)
	70-80	1.4 (0.8-2.2)	1.2 (0.6-2.2)	1.1 (0.5-2.0)	2.3 (1.2-4.6)
	80-90	1.1 (0.6-2.1)	0.8 (0.3-1.8)	1.4 (0.6-2.9)	1.0 (0.4-2.3)
	overall	1.5 (1.1-2.1)	1.2 (0.7-1.8)	1.4 (0.9-2.2)	2.1 (1.3-3.4)

* Adjusted for age, sex, diabetes mellitus, body mass index, smoking behavior.
† Represents the upper quintile of the white matter lesions severity distribution.
‡ Hypertension: systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥95 and/or the use of blood pressure lowering drugs.

Discussion

We studied the effect of hypertension, its duration and its treatment status on cerebral white matter lesions in a prospective, population-based study among elderly subjects. We found that current hypertension, and hypertension established 5 or 20 years ago, was associated with the presence of white matter lesions, subcortical as well as periventricular. In addition, our results suggest that effective treatment reduces the risk for both types of white matter lesions, compared with ineffective treatment.

When a risk factor such as hypertension is associated with increased mortality,[14] the association between hypertension earlier in life and white matter lesions later in life is likely to be biased by selective mortality, especially with advancing ages. This selective mortality is a particular concern in the Zoetermeer Study sub-population, in which follow-up was longest. We addressed this issue by comparing the prevalence of hypertension in three age strata between survivors and those who had died before the follow-up. Indeed, in the youngest age stratum there was no significant difference for hypertension between survivors and those who had died before the follow-up, whereas this difference was significantly different in the highest age categories. It seems therefore plausible to argue that relative risks in the youngest age category represent the most unbiased risk estimates. In the Rotterdam Study sub-population selective survival plays a less prominent role because baseline data collection was already relatively late in life and the follow-up period was short (5 years). Therefore it seems plausible that individuals with long-lasting hypertension would have died before baseline collection of the Rotterdam Study. In addition to this, selection bias may have influenced our findings, especially in the oldest age category where the response rate was lowest, as subjects who refused to participate had higher systolic blood pressures than participants at baseline did. The relative risk for white matter lesions with hypertension in the two higher age strata may have been underestimated, by a decreased susceptibility to the effects of hypertension among survivors, and by selective non-participation of survivors with white matter lesions and cognitive impairment.

How hypertension exactly contributes to white matter lesions remains to be elucidated. A possible explanation can be that long-standing hypertension results in a decrease in cerebral blood flow by impairment of the cerebral autoregulation.[15] The cerebral blood flow is maintained in healthy subjects at a constant level between blood pressure levels in the order of 60-150 mm Hg.[15] However, these limits shift upward in subjects with chronic hypertension and this may lead to transient decreases in

cerebral blood flow during periods of lower blood pressure, even at blood pressure levels considered normal for normotensive subjects.[16-18] Most vulnerable are areas with an already marginal blood supply under physiological conditions, such as the subcortical and periventricular white matter.[19,20] As a consequence the white matter, of chronic hypertensives might suffer from ischemia during episodes of a relatively low blood pressure. This is in line with the observation of severe periventricular white matter lesions in hypertensive subjects who have an impaired cerebral autoregulation,[18] and with our observation of the strongest associations in subjects with the longest duration of hypertension.

The association between hypertension treatment status and white matter lesions may be confounded by differences in actual blood pressure levels or in duration (severity) of hypertension between the groups. For example, blood pressure levels in untreated subjects may be lower than in those treated and controlled, thereby explaining the lower risk for white matter lesions. However, we found much lower systolic and diastolic blood pressures in treated controlled persons than in the untreated. We therefore consider it unlikely that the higher risk for white matter lesions among the treated and controlled can be explained by higher levels of current blood pressure. Another potential source of bias is a different duration of hypertension among the groups. The reason that an untreated hypertensive subject does not receive blood pressure lowering drugs may be that hypertension had been present for a relatively short period of time and had not yet been detected. Therefore they may be at lower risk for having white matter lesions. Indeed we showed that among untreated hypertensives the proportion of subjects with a shorter duration of hypertension was relatively high. However, we consider it unlikely that this bias has influenced the associations for the two treated groups, because they were all treated during the follow-up, and as there was no major difference in the duration of hypertension between the treated controlled and treated uncontrolled subjects.

A possible explanation for our finding that treated, but uncontrolled hypertensives have the highest risk for either type of white matter lesion may be that adequate control of hypertension may lead to a lower risk of cerebral arteriolosclerosis and thereby prevent the occurrence of cerebral ischemia. [2,20] A recent clinical trial of antihypertensive drugs in systolic hypertension showed a reduced incidence of dementia in the treated group;[10] this may be through sparing of white matter, although this aspect was not studied.

In conclusion, we found that a 20 year duration of hypertension increased the risk for white matter lesions about 20-fold. Effective treatment of hypertension reduces the proportion of white matter lesions. This

offers potential therapeutic possibilities in preventing and reducing the development of white matter lesions and the attendant cognitive decline or dementia.

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Chapter 4

Atherosclerosis and cerebral white matter lesions

4.1 Aortic atherosclerosis at middle age predicts cerebral white matter lesions in the elderly

Abstract

Background *Magnetic resonance imaging 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 mid-life and late-life and cerebral white matter lesions.*

Methods *We randomly sampled subjects aged between 60-90 years from two population-based follow-up studies in which subjects had their baseline examinations in 1975-1978 (mid-life) and in 1990-1993 (late-life). In 1995-1996 subjects underwent 1.5T MRI-scanning; white matter lesions were rated in the deep subcortical and periventricular regions separately. Aortic atherosclerosis was assessed on abdominal X-rays that were obtained from 277 subjects in midlife and 536 subjects in late-life.*

Findings *The presence of aortic atherosclerosis during mid-life was significantly associated with the presence of periventricular white matter lesions approximately 20 years later (adjusted relative risk 2.6; 95% CI 1.3-5.2); this relation was dose dependent. No association was found between mid-life aortic*

atherosclerosis and subcortical white matter lesions (adjusted relative risk 1.1; 95% CI 0.5-2.3), nor between late-life aortic atherosclerosis and white matter lesions.

Interpretation *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.*

Introduction

Cerebral magnetic resonance imaging (MRI) scans of elderly, non-demented people frequently show white matter lesions.[1-3] There is evidence that white matter lesions are associated with cognitive decline and dementia.[2,4-6] We previously showed an association between atherosclerosis and white matter lesions in a small cross-sectional population-based study among elderly subjects.[7] However, atherosclerosis is a gradual process, which already starts in the first decades of life, when prevalence of white matter lesions is very low.[8-11] If atherosclerosis early in life is a predictor for white matter lesions in later years, intervention in early life might help prevent cognitive decline and possibly dementia. Aortic calcification observed on an abdominal X-ray 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.[12-15] Cerebral white matter lesions can be located in the periventricular or the subcortical region. It is not known whether these two types of lesions have the same causes. It has been suggested that especially severe periventricular white matter lesions are associated with impaired cognitive performance.[6]

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

Methods

Study population

The Rotterdam Scan Study was designed to study determinants and the consequences of cerebral white matter lesions in the elderly. In 1995-1996, 1904 subjects aged between 60-90 years were randomly selected in

strata of age (5 years) and sex from two large ongoing prospective follow-up cohort studies that had their baseline examinations during subjects' mid-life (the Zoetermeer Study) or late-life (the Rotterdam Study). Mean age of subjects during mid-life was 53.7 years (SD 5.5) years and during late-life 68.7 years (SD 8.0). The Zoetermeer Study had its baseline data collection in 1975-1978; the mean follow-up period since then was 19.6 years. The Rotterdam Study had its baseline data collection from 1990-1993; the mean follow-up period was 4.8 years. The Zoetermeer Study is a population-based follow-up study among 10361 subjects, aged between 5-91 years, 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 aged 55 years and over, which focuses on determinants of neurological, cardiovascular, locomotor and ophthalmologic disorders in the elderly. Both studies have been described in detail elsewhere.[16,17]

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 contra-indications was reviewed in order to assess eligibility (dementia; blindness; or presence of MRI contra-indications, including prosthetic valves, pacemaker, cerebral aneurysm clips, intra-ocular metal fragments, cochlear implants and claustrophobia). From 1904 invited subjects 1724 were eligible. Complete information, including a cerebral MRI scan was obtained from 1084 persons (response 63%); 568 from the Rotterdam Study (response 68%) and 516 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 X-rays were taken in subjects of 45 years and over at the time of baseline data collection of the Zoetermeer Study (response 82%). From 305 subjects out of the 401 subjects in our study who were aged over 45 years at the time of baseline data collection, a lateral abdominal X-ray had been obtained. During the follow-up study (1995-1996) X-rays of 277 subjects could be retrieved. Abdominal X-rays were also obtained during the baseline examination of the Rotterdam Study. From 536 of our participants an abdominal X-ray had been obtained (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. Severity of atherosclerosis was rated as mild when deposits were between 0-1 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 sub-populations of the Rotterdam Scan Study. Height and weight were measured without shoes in light clothing. The body mass index was calculated as weight divided by height square. Blood pressure was measured two times on the right arm by means of a random zero sphygmomanometer in 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 anti-diabetics or insulin (both sub populations) or if the random or post load glucose level was higher than 11.1 mmol/l (subjects originating from the Rotterdam Study).[18] Serum total cholesterol was measured by an automated enzymatic method.[19]

MRI Scanning protocol

From all participants an axial T1, T2 and PD weighted cerebral MRI scan was made on a 1.5T MRI scan. Subjects recruited from the Zoetermeer Study were scanned with a 1.5T MR Gyroscan (Philips, Best, The Netherlands) and participants from the Rotterdam Study were scanned with a 1.5T MR Vision (Siemens, Erlangen, Germany). In order to provide comparability the following pulse sequences were applied: at 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 at the Vision T1 (TR 485 ms, TE 14 ms), T2 (TR 2236, TE 90 ms) and PD (TR 2236 ms, TE 20 ms). Slice thickness was 6 mm and 5 mm respectively, with an inter-slice gap of 20.0%. The images were printed on hard copy with a reduction factor of 2.7.

White matter lesions rating scale

White matter lesions were considered present if visible as hyperintense on both proton density (PD) and T2 weighted images and not hypointense on T1 weighted image. White matter lesions were distinguished into deep subcortical and periventricular regions. The number and size of deep subcortical white matter lesions was rated on hard copy according to their largest diameter in categories of small (<3 mm), medium (3-10 mm) or large lesions (>10 mm). In order 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 semi-quantitatively 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), 1 (pencil-thin periventricular lining), 2 (smooth halo or thick lining) to 3 (large confluent white matter lesions). The overall degree of periventricular white matter lesions was calculated by adding up the scores for the three separate categories (range 0-9).

All MRI scans were examined by two raters from a pool of four experienced raters. In case of a disagreement of more than one point, a consensus reading was held; in all other cases the readings of both readers were averaged. The inter- and intra-rater studies showed a good to excellent agreement. Weighted kappas for grading the periventricular white matter lesions were between 0.79-0.90. For total deep subcortical white matter volume the inter-reader and intra-rater 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. 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 presence of severe white matter lesions. Subjects without severe white matter lesions were the reference group (lower four quintiles). The association between mid-life 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 severity of aortic atherosclerosis and white matter lesions was studied by creating dummy variables for the extent of aortic atherosclerosis. Additional adjustments were made for possible baseline confounding factors including body mass index, total serum cholesterol, diabetes mellitus, hypertension and smoking (never, former or current). The relative risks are presented with a 95% confidence interval (95% CI).

Results

Table 1 shows the baseline characteristics of the study population. The overall response rate was 62.9%, and declined from 73% among subjects

Table 1
Characteristics of participants in the Rotterdam Scan Study during mid-life (assessment 1975-1978) and late-life (assessment 1990-1993)*

Characteristic	Mid-life assessment	Late-life assessment
Number of subjects	277	536
Women (%)	57.5	48.9
Mean age (years)	53.8 (5.5)	68.7 (8.0)
Mean age at MRI (1995-1996)	73.3 (5.5)	73.4 (7.9)
Body Mass Index (kg/m^2)	25.3 (2.9)	26.3 (3.4)
Systolic BP (mm Hg)	133.8(17.3)	136.7 (20.7)
Diastolic BP (mm Hg)	82.4 (10.7)	73.2 (10.8)
Serum cholesterol (mmol/l))	6.2 (1.1)	6.7 (1.2)
Aortic atherosclerosis (%)	21.3	58.6
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.

Table 2
The relative risk (95% CI) of severe white matter lesions* associated with mid-life and late-life aortic calcification.

	Aortic calcification in mid-life		Aortic calcification in late-life	
	absent	present	absent	present
Number of subjects	218	59	222	314
Periventricular white matter lesions				
Model 1	1.0 (ref)	2.5 (1.3-4.8)	1.0 (ref)	0.9 (0.6-1.4)
Model 2	1.0 (ref)	2.6 (1.3-5.2)	1.0 (ref)	1.0 (0.6-1.7)
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)

*Dichotomized at the upper quintile of the severity distribution of white matter lesions
Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, baseline presence of diabetes mellitus, hypertension, smoking behaviour, serum cholesterol, body mass index.

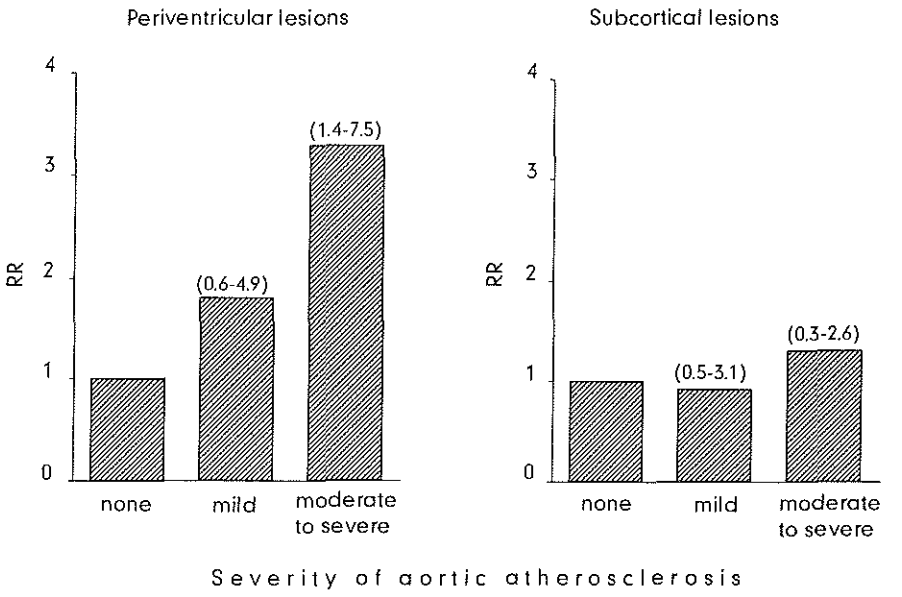

Figure 1
The association between mid-life severity of aortic atherosclerosis and presence of severe white matter lesions 20 years later (relative risks, with 95% CI given in parentheses).

aged between 60-70 years to 48% among participants aged between 80-90 years in 1995-1996. Non-participants 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 <0.01, respectively). There was no significant difference according to sex, diastolic blood pressure and the prevalence of aortic calcification or hypertension at baseline. Non-participants from the Zoetermeer Study had a higher systolic blood pressure (135.3 mm Hg versus 132.8 mm Hg; p=0.05) at baseline compared to participants, whereas this was not significantly different for subjects from the Rotterdam Study.

Prevalence of aortic atherosclerosis was 21% at mid-life and 59% at late-life. During mid-life, in 218 subjects there was no aortic atherosclerosis, whereas mild and moderate-to-severe aortic atherosclerosis was observed in 25 and 34 subjects, respectively. During late-life, there were 192 subjects without any aortic atherosclerosis, whereas mild and moderate-to-severe aortic atherosclerosis was observed in 99 and 175 subjects, respectively. At follow-up, 21% 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 mid-life is significantly associated with the presence of severe periventricular white matter lesions 20 years later (RR 2.6; 95% CI 1.3-5.2), but not with deep subcortical white matter lesions (RR 1.1; 95% CI 0.5-2.3). These associations were similar for men and women. In contrast, presence of aortic atherosclerosis during late-life was not associated with either type of white matter lesion.

Figure 1 shows a dose dependency between the extent of aortic atherosclerosis in mid-life 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 atherosclerosis in late-life the relative risks of having periventricular white matter lesions were 1.0 (95% CI 0.5-1.9) and 0.7 (95% CI 0.4-1.3), and for deep subcortical white matter lesions 1.2 (95% CI 0.6-2.3) and 0.8 (95% CI 0.4-1.4), respectively. Again there were no major sex differences in these associations.

Discussion

We found a dose-dependent relation between severity of aortic atherosclerosis during mid-life 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. Yet, we consider it unlikely that selection bias has played a major role in our study since there were only small, non-significant, differences between participants and non-participants. We cannot exclude that our relative risks are somewhat underestimated because we performed our study in survivors of the two baseline studies. Subjects who had died between baseline examination and follow-up may have had more severe aortic atherosclerosis compared to those who survived.

Another limitation is that there was no neuro-imaging 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, in an autopsy study it was shown that radiographically detected aortic calcification represented true intimal atherosclerosis.[12] When compared with computed tomography it was shown that calcifications seen at the X-ray were in the vessel wall in all cases.[20]

The association between aortic atherosclerosis and cerebral white matter lesions was found only for aortic plaques in mid-life, and not for those found in late-life. The explanation may be that subjects who already had mild or severe aortic atherosclerosis during mid-life, 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. This interpretation is supported by our finding that severity of aortic atherosclerosis is associated with the presence of white matter lesions in a dose-dependent fashion. Another explanation for the weak association between late-life aortic atherosclerosis and white matter lesions might be that in elderly subjects presence of atherosclerosis has less discriminative power because many other risk factors for white matter lesions co-exist.

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. As the periventricular white matter is an arterial border zone, already marginally perfused under physiological circumstances, it is especially vulnerable by a decrease of cerebral blood flow.[21-23] In contrast, the subcortical white matter is not an arterial watershed area.[24] Atherosclerosis induces hyalinisation, tortuosity and elongation of vessels in the periventricular white matter.[22,25-27] This may contribute to a decrease in blood flow in the periventricular white matter, leading to ischemia.[22] This explanation is supported by studies that found an association between periventricular white matter lesions and atherosclerosis-related factors as hypertension, diabetes mellitus, and presence of silent infarcts.[28]

In conclusion, our study shows that aortic atherosclerosis during mid-life is a major risk factor for periventricular white matter lesions in the brain at older 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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4.2 Carotid or peripheral atherosclerosis and cerebral white matter lesions

Abstract

Introduction *Cerebral white matter lesions are frequently observed on MRI scans of elderly, non-demented people. There is evidence that white matter lesions are involved in the pathophysiology of cognitive decline and dementia. White matter lesions can be distinguished into those in the periventricular or in the subcortical region. Pathological and epidemiological studies have suggested involvement of atherosclerosis in the pathogenesis of these lesions. Our study reports on the association between indicators of atherosclerosis at different sites and white matter lesions in a population based study among 1084 elderly subjects.*

Methods *We randomly sampled 1084 subjects aged between 60-90 years from two prospective population-based studies. All subjects underwent ultrasonography of the carotid artery; also the ankle-to-brachial index was measured. In addition 1.5T MRI-scanning was performed; white matter lesions in the subcortical and periventricular regions were rated separately.*

Results *Presence of plaques in the carotid artery was significantly associated with periventricular white matter lesions (p_{trend}=0.03), but not with the subcortical white matter lesions (p_{trend}=0.18). The intima media thickness was associated (borderline significance) with periventricular white matter lesions*

(p_{trend}=0.06), but not with subcortical white matter lesions (p_{trend}=0.73). There was no association between the ankle-to-brachial index and periventricular white matter lesions or subcortical white matter lesions.

Conclusion *We found an association between atherosclerosis of the carotid artery and especially periventricular white matter lesions. This may underlie findings of a relation between atherosclerosis and dementia. Carotid atherosclerosis (a site near the brain) may be a better marker for cerebral arteriolosclerosis, than peripheral arterial disease.*

Introduction

Cerebral white matter lesions are frequently observed on magnetic resonance imaging (MRI) scans of elderly, non-demented people.[1-3] There is evidence that white matter lesions are involved in the pathogenesis of cognitive decline and dementia.[2,4-6] In addition there is evidence for a relation between atherosclerosis and dementia.[7] White matter lesions can anatomically be distinguished into lesions located in the periventricular and in the deep subcortical region. It is not known whether these different white matter lesions have the same causes, but pathological and epidemiological studies have indicated an important role of arteriolosclerosis in the white matter as an intermediate factor.[8-12] Nowadays, several non-invasive techniques for detecting early stages of atherosclerosis at different arterial sites are available. High resolution B-mode ultrasonography of the carotid artery can visualize plaques and the intima-media thickness (arterial wall thickness),[13,14] whereas the ankle-to-brachial index represents atherosclerosis of the lower arteries.[15] There are no studies available that have related these indicators with the two types of white matter lesions over their full range of severity. In this study we report the association between indicators of atherosclerosis at two different sites and white matter lesions, in a population-based study among 1084 elderly subjects.

Methods and subjects

Study population

The Rotterdam Scan Study was designed to study determinants and consequences of age related brain abnormalities in the elderly. In 1995-1996, 1904 subjects aged between 60-90 years were randomly selected in strata

of age (5 years) and sex from two large ongoing prospective follow-up cohort studies, the Zoetermeer Study and the Rotterdam Study. The Zoetermeer Study had its baseline data collection from 1975-1978; the mean follow-up period was 19.6 years. For the Rotterdam Study the baseline data-collection took place from 1990-1993; the mean follow-up period was 4.8 years. Both studies have been described in detail elsewhere.[16,17] In short, the Zoetermeer Study is a prospective population-based study among 10361 subjects, aged between 5-91 years at baseline; it originally addressed determinants of chronic diseases. The Rotterdam Study is a population-based prospective cohort study, among 7983 elderly subjects aged 55 years and over, which studies determinants of neurological, cardiovascular, locomotor and ophthalmologic diseases in the elderly.

For the follow-up examination in the Rotterdam Scan Study subjects were invited by letter, and subsequently contacted by telephone. Upon agreement to participate in the study a list of contraindications was reviewed in order to assess eligibility (dementia; blindness; or presence of MRI contraindications, including prosthetic valves, pacemaker, cerebral aneurysm clips, a history of intra-ocular metal fragments, cochlear implants and claustrophobia). From 1904 invited subjects 1724 were eligible. Complete information, including a cerebral MRI scan, was obtained from 1084 persons (response rate 63%); 568 from the Rotterdam Study (response rate 68%) and 516 from the Zoetermeer Study (response rate 58%). The overall response rate was 63%, and declined from 73% among subjects aged between 60-70 years to 48% among those aged between 80-90 in 1995-1996. Each participant signed an informed consent form. The study was approved by the medical ethics committee of the Erasmus University.

Measurement of atherosclerosis

Carotid arteries

In each subject ultrasonography of both carotid arteries was performed with a 7.5 MHz linear array transducer and a Duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, WA). For subjects originating from the Rotterdam Study baseline carotid ultrasonography was available. The carotid arteries were evaluated for the presence (yes/no) of atherosclerotic lesions (plaques), defined as a focal widening relative to adjacent segments, with protrusion into the lumen of only calcified deposits or a combination of calcifications and non-calcified material. This measurement was performed for the left- and right-sided common carotid artery, bifurcation and internal carotid artery, both at the anterior and posterior wall, leading to a total plaque score ranging from 0-

12. The intima-media thickness of the common carotid wall (wall thickness) was measured on a longitudinal 2-dimensional ultrasound image of the carotid artery. The near and far walls of the carotid artery are displayed as two bright white lines, separated by a hypo-echogenic space. The distance of the leading edge of the first bright line on the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness.[18,19] The actual measurement of the intima-media thickness was performed off-line and was performed only in subjects from the Rotterdam Study, and only at baseline. The mean intima-media thickness of the near and far wall of the common carotid atery wal was used in the analysis. However, we consider this a good reflection of current intima-media thickness since rate of progression of this measurement is about 0.010 mm/year or 0.006 mm/year, in subjects with or without carotid artery plaques, respectively.[20]

Ankle-to-brachial index

The presence of atherosclerosis in the arteries of the lower limbs was assessed by means of the ankle-to-brachial index. From subjects originating from the Rotterdam Study baseline ankle-to-brachial index measurements were available as well. The ankle-to-brachial index was computed by measuring blood pressure in the tibial artery using an 8 MHz continuous wave Doppler probe (Huntleigh 500D, Huntleigh Technology, Bedfordshire, UK) and a random zero sphygmomanometer, with the participant supine. Blood pressure was measured on the right arm by means of a random zero sphygmomanometer in sitting position. The ankle-to-brachial index was defined as the systolic blood pressure measured at both the left and right posterior tibial artery divided by the systolic blood pressure of the right arm. The lowest ankle-to-brachial index in either leg was used in the analyses. Subjects with an ankle-to-brachial index less than 0.9 were considered to suffer from peripheral arterial disease.[21,22]

Measurement of other covariates

The body mass index was calculated as weight divided by height square. Information on smoking was obtained with a standardized questionnaire, which was checked by a physician during the interview. Diabetes mellitus was considered to be present if the participant was taking oral anti diabetics or insulin.

MRI Scanning protocol

From all participants an axial T1, T2 and PD weighted cerebral MRI scan was made on a 1.5T MRI scan. Subjects recruited from the Zoetermeer Study were scanned with a 1.5T MR Gyroscan (Philips, Best, The Netherlands) and participants from the Rotterdam Study were scanned with a 1.5T MR Vision (Siemens, Erlangen, Germany). In order to provide comparability the following pulse sequences were applied: at 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 at the Vision T1 (TR 485 ms, TE 14 ms), T2 (TR 2236, TE 90 ms) and PD (TR 2236 ms, TE 20 ms). Slice thickness was 6 mm and 5 mm respectively, with an inter-slice gap of 20.0%. The images were printed on hard copy with a reduction factor of 2.7.

White matter lesions rating scale

White matter lesions were considered present if these were hyper-intense on both PD and T2 weighted images and not hypo-intense on T1 weighted images. White matter lesions were distinguished into those in the subcortical or periventricular regions. The number and size of subcortical white matter lesions was rated on hard copy according to their largest diameter, in categories of small (<3 mm), medium (3-10 mm) or large lesions (>10 mm). In order to calculate the volume of subcortical white matter lesions on hard copy, the lesions were considered to be spherical with a fixed diameter per size category. Periventricular white matter lesions were rated semi-quantitatively per region: adjacent to the frontal horns (frontal capping); adjacent to the wall of the lateral ventricles (bands), and adjacent to the occipital horns (occipital capping), on a scale ranging from 0 (no white matter lesions), 1 (pencil-thin periventricular lining), 2 (smooth halo or thick lining) to 3 (large confluent white matter lesions). The overall degree of periventricular white matter lesions was calculated by adding up the scores for the three separate categories (range 0-9). All MRI scans were examined by two raters from a pool of four experienced raters. In case of disagreement by more than one point, a consensus reading was held; in all other cases the readings of both readers were averaged. The inter- and intra-rater studies showed good to excellent agreement. Weighted kappas for grading the periventricular white matter were between 0.79-0.90. For total subcortical white matter volume the inter- and intra-rater intra-class correlation coefficient was 0.88 and 0.95, respectively.

Data analyses

The relation between indicators of atherosclerosis and white matter lesions was assessed by means of age and sex adjusted analysis of covariance (ANCOVA); we obtained the mean grade of periventricular white matter lesions or the mean volume of subcortical white matter lesions (milliliter, (ml)) per quintile of the distribution of the intima-media thickness, the carotid artery plaques and the ankle-to-brachial index. In addition we calculated the mean grade of the periventricular white matter lesions or the mean volume of subcortical white matter lesions for subjects with or without peripheral arterial disease. Additional adjustments were made for body-mass-index (continuous), smoking (never, former or current) and diabetes mellitus (dichotomous).

Results

Table 1 presents characteristics of the study population. At follow-up, 20% and 8% of all participants were without any periventricular or subcortical white matter lesions, respectively. The median volume of subcor-

Table 1
Characteristics of the study population in 1995/1996 (at MRI assessment)*

Number of subjects	1084
Age (yrs)	72.3 (7.4)
Women (%)	52.0
Body Mass Index	26.6 (4.0)
Diabetes Mellitus (%)	6.9
Smokers	
Current (%)	17.7
Former (%)	44.7
Never (%)	37.6
Systolic BP (mm Hg)	147.3 (21.6)
Diastolic BP (mm Hg)	78.7 (11.7)
Hypertension (%)	51.3
Indicators of atherosclerosis	
Intima media thickness (mm)†	0.76 (0.13)
Plaques carotid arteries (%)	62.3
Ankle-to-brachial index	1.1 (0.2)
Peripheral arterial disease (%)‡	16.6

* Values are unadjusted means (SD) or percentages.
† Only measured in the Rotterdam Study at baseline (1990-1993).
‡ Defined as an ankle-to-brachial index below 0.9.

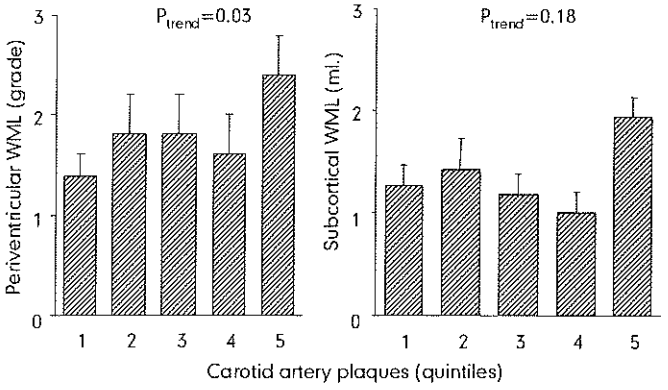

Figure 1 – The association between carotid artery plaques (in quintiles of the distribution) and periventricular (mean grade) and subcortical (mean volume) white matter lesions (SE), adjusted for age, sex, body-mass index, smoking and diabetes mellitus.

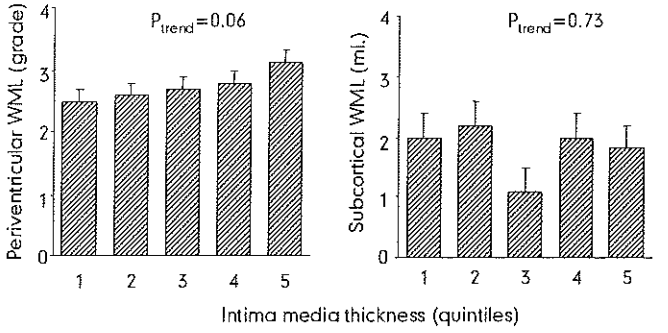

Figure 2 – The association between intima-media thickness (in quintiles of the distribution) and periventricular (mean grade) and subcortical (mean volume) white matter lesions (SE), adjusted for age, sex, body-mass index, smoking and diabetes mellitus.

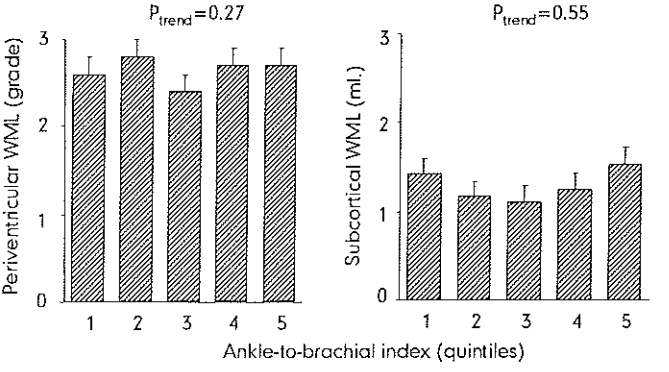

Figure 3 – The association between ankle-to-brachial index (in quintiles of the distribution) and periventricular (mean grade) and subcortical (mean volume) white matter lesions (SE), adjusted for age, sex, body-mass index, smoking and diabetes mellitus.

tical white matter lesions on hard copy was 3.8 ml and the median grade of periventricular white matter lesions was 2 (on a scale from 0-9). Both median volume of subcortical white matter lesions and mean grade of periventricular white matter lesions increased significantly with age. Responders originating from the Rotterdam Study were significantly younger than non-responders (mean age 68.9 versus 71.1 years, $p<0.001$), had a lower carotid intima media thickness (0.76 versus 0.78 mm, $p=0.05$) and had a higher ankle-to-brachial index (1.07 versus 1.09, $p=0.02$). There was no significant difference between carotid plaques at baseline in responders versus non-responders in the Rotterdam Study (mean 1.7 plaques in both groups, $p=0.75$). These baseline data were not available in the Zoetermeer Study.

At follow-up, 20% and 8% of all participants were without any periventricular or subcortical white matter lesions, respectively. Median volume of deep subcortical white matter lesions on hard copy was 3.9 ml and the median grade of periventricular white matter lesions was 2. Both the median volume of deep subcortical white matter lesions and the mean grade of periventricular white matter lesions increased significantly with age.

The intima media thickness (Rotterdam Study) was associated with periventricular white matter lesions, the trend almost reaching statistical significance ($p_{trend}=0.06$), but not with the subcortical white matter lesions ($p_{trend}=0.73$; figure 1). Presence of plaques in the carotid artery was significantly associated with periventricular white matter lesions ($p_{trend}=0.03$), but not with subcortical white matter lesions ($p_{trend}=0.18$; figure 2). There was no association between the ankle-to-brachial index and either periventricular white matter lesions or subcortical white matter lesions (figure 3). In addition there was no significant difference between subjects with or without peripheral arterial disease in the mean grade of periventricular white matter lesions (2.6 (SD 2.0); for both groups) and the mean volume of subcortical white matter lesions (1.6 ml. (SD 2.0) and 2.0 ml. (SD 3.2)), respectively. These associations were similar if the analysis were performed for the Rotterdam and Zoetermeer Study separately.

Discussion

We found a clear, dose-dependent relationship between the severity of intima-media thickness or the presence of plaques in the carotid artery on the one hand and periventricular white matter lesions on the other. These associations were much less clear for subcortical white matter lesions. There was no association between the ankle-to-brachial index and either

type of white matter lesions. There was no significant difference in severity of periventricular and subcortical white matter lesions between subjects with or without peripheral arterial disease.

The strength of this study is its large number of elderly subjects from the general population, including institutionalized persons. However, some limitations and methodological issues need to be discussed. There were significant differences in baseline age and indicators of atherosclerosis between responders and non-responders, at least in the Rotterdam Study (for the Zoetermeer study there were no such baseline indicators of atherosclerosis available). However, we consider it unlikely that the relation between atherosclerosis and white matter lesions is different in non-responders than in responders from the Zoetermeer Study than in those from the Rotterdam Study. This is supported by our findings of similar associations between all indicators of atherosclerosis and white matter lesions in the two sub-populations. Another limitation is that there was no neuro-imaging available at baseline of the study. This makes it difficult to investigate a temporal relation between atherosclerosis and white matter lesions.

An important point is the validity of the atherosclerosis measurements. Increased carotid intima-media thickness may not necessarily reflects atherosclerosis. It may merely reflect a physiological adaptation of the vessel wall in a response to mechanical stress, secondary to variations in flow or wall tension. [23] However, in several studies ultrasonographically detected increases in carotid wall thickness and its progression were found to be associated with cardiovascular risk factors.[13,24-26] These findings support the idea that increased carotid wall thickness, as detected by ultrasonography, reflects a valid index of atherosclerosis.

All atherosclerosis indicators were based on single measurements. This may have led to misclassification. However, all atherosclerosis assessments were done without prior knowledge of the degree of white matter lesions; therefore we consider it unlikely that this misclassification is related to the extent of white matter lesions. Any measurement error was likely to be random, and would have biased our findings towards the null hypothesis, leading to an underestimation of the strength of the associations.

The association between indicators of atherosclerosis in the carotid arteries and white matter lesions was most marked for periventricular white matter lesions. There was no association between ankle-to-brachial index and any type of white matter lesions. This might be explained by the fact that the ankle-to-brachial index is a ratio of two systolic blood pressures, and may lead to spurious associations,[27] especially in subjects with a high systolic blood pressure. In contrast, ultrasonographically de-

tected carotid wall thickness and plaques are a reflection of the atherosclerotic state of the carotid artery and might therefore be a more valid indicator of atherosclerosis. [28, 29]

We found a significant dose-dependent association of periventricular white matter lesions with intima media thickness and carotid artery plaques, but not for with subcortical white matter lesions. This suggests that different pathophysiological events underlie periventricular and subcortical white matter lesions, possibly related to vascularization. As the periventricular white matter is marginally perfused under physiological circumstances it is especially vulnerable by a decrease of cerebral blood flow.[12,30,31] Atherosclerosis induces hyalinization, tortuosity and elongation of vessels in the periventricular white matter.[9,12,32,33] These arteriolar changes may contribute to a decrease in blood flow in the periventricular white matter, leading to ischemic damage.[12] This notion is supported by studies that found an association between specifically periventricular white matter lesions and atherosclerosis related factors as hypertension, diabetes mellitus, presence of silent infarcts.[34, 35]

In conclusion, we found an association between indices of atherosclerosis in the carotid artery and periventricular white matter lesions, whereas this was not found for subcortical white matter lesions. This may have implications for the relation between atherosclerosis and dementia.[7] There was no relation between both types of lesions and peripheral arterial disease. Carotid atherosclerosis (a site near the brain) may better reflect cerebral atherosclerosis and arteriolosclerosis, than peripheral arterial disease, which probably represents a more general marker of atherosclerosis.

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4.3 Atrial fibrillation and cerebral white matter lesions

Abstract

Background *Cerebral white matter lesions are often observed on MRI scans of elderly non-demented and demented persons. Their pathogenesis is not fully understood but cerebral hypoperfusion may be involved. Atrial fibrillation is a common finding in elderly subjects and may lead to a reduced cardiac output with cerebral hypoperfusion. We investigated the association between atrial fibrillation and the presence of white matter lesions.*

Methods *In 1995-1996 we randomly sampled 1084 subjects from two ongoing prospective population based studies. From each participant an ECG was recorded; atrial fibrillation and left ventricular hypertrophy were diagnosed with a computer program. For one of the two groups (558 subjects) earlier ECGs were available (mean follow-up 4.7 years). All subjects underwent 1.5T MRI-scanning; white matter lesions were separately rated for the periventricular and subcortical region.*

Results *The prevalence of atrial fibrillation was 1.9% among subjects under the age of 75 years and 5.5% in subjects over the age of 75 years. Subjects with atrial fibrillation had more than twice as often severe periventricular white matter lesions (RR 2.5; 95%CI 1.1-5.6) but no increased risk of subcortical white matter lesions (RR 1.3; 95% CI 0.6-3.1). For 8 persons with atrial fibrillation and left ventricular hypertrophy these figures were 6.7 (95%CI 0.6-74.2) and 2.0 (95%*

CI 0.5-8.0), respectively. For subjects with atrial fibrillation both at baseline and at follow up the relative risks were 7.0 (95%CI 1.3-39.6) and 0.8 (95% CI 0.2-3.9), respectively.

Conclusions *Atrial fibrillation is associated with periventricular white matter lesions, but not with subcortical white matter lesions. Effective treatment of atrial fibrillation may possibly reduce the development of white matter lesions and of the attendant cognitive decline or dementia.*

Introduction

White matter lesions are often observed on cerebral magnetic resonance imaging (MRI) scans of elderly, non-demented persons.[1-3] Evidence is accumulating that these white matter lesions play an important role in the development of cognitive decline and dementia.[3-6] Their pathogenesis is not fully understood, but cerebral hypo-perfusion may be involved.[7-9]

Atrial fibrillation is a common finding among the elderly and could lead to a reduced cardiac output, resulting in cerebral hypo-perfusion.[10-12] Atrial fibrillation has been associated with cognitive function,[13] and dementia.[14] It is possible that not only large infarcts from embolism to the brain, but also white matter lesions underlie this association.[14]

White matter lesions can be distinguished according to their location in the periventricular and the subcortical region. It has been suggested that especially periventricular white matter lesions are associated with impaired cognitive performance.[6] Because of its terminal arterial supply the periventricular white matter is especially vulnerable to a reduction in cerebral blood flow.[9,15,16] To date, only a few, and relatively small, population based studies have addressed the relation between atrial fibrillation and white matter lesions.[17,18]

In the current study we investigated the association between atrial fibrillation and presence of cerebral white matter lesions in a population-based study among the elderly. We hypothesized that atrial fibrillation would be associated with white matter lesions, in particular in the periventricular region.

Methods

Study population

The Rotterdam Scan Study was designed to study determinants and cognitive consequences of age related brain abnormalities in the elderly. In

1995-1996, 1904 subjects aged between 60-90 years were randomly selected in strata of age (5 years) and sex from two large ongoing prospective follow-up cohort studies, the Zoetermeer Study and the Rotterdam Study. The Zoetermeer Study had its baseline data-collection from 1975-1978, whereas the Rotterdam Study had the baseline data-collection from 1990-1993. Both studies have been described in detail elsewhere.[19,20] In short, the Zoetermeer Study is a prospective population based study among 10361 subjects, aged between 5-91 years at baseline, which originally aimed at identifying determinants of chronic diseases. The Rotterdam Study is a population based prospective cohort study, among 7983 elderly subjects aged 55 years and over, which addresses determinants of neurological, cardiovascular, locomotor and ophthalmologic diseases in the elderly.

For the follow-up examination in the Rotterdam Scan Study subjects were invited by a letter, and subsequently contacted by telephone. Upon agreement on participation in the study a list of contraindications was reviewed in order to assess eligibility (dementia; blindness; or presence of MRI contraindications, including prosthetic valves, pacemaker, cerebral aneurysm clips, a history of intra-ocular metal fragments, cochlear implants and claustrophobia). Of 1904 invited subjects, 1724 were eligible. Complete information, including a cerebral MRI scan, was obtained from 1084 persons (response 63%); 568 from the Rotterdam Study (response 68%) and 516 from the Zoetermeer Study (response 58%). The response rate declined from 71% among subjects aged under 75 years to 52% among participants aged over 75 years in 1995-1996. Non-responders were significantly older. Each participant signed an informed consent form. The study was approved by the medical ethics committee of the Erasmus University.

Measurement of atrial fibrillation

As part of the data-collection in the Rotterdam Scan Study a 12-lead ECG was recorded and stored digitally by means of an ACTA electrocardiograph (ESAOTE, Florence, Italy) in 960 subjects. Eleven percent of all subjects had a missing ECG at follow up, mostly for technical reasons (disturbances in power supply or technical problems with the recorder). At baseline, ECGs had also been obtained, in a similar way, in the Rotterdam Study (mean follow-up 4.7 years; n=558), but not in the Zoetermeer Study. All ECGs were processed by the Modular ECG Analysis System (MEANS).[21] The program provides a rhythm and contour interpretation, and has been extensively evaluated.[21-23] For atrial fibrillation, left ven-

tricular hypertrophy and myocardial infarction the MEANS interpretation was used.

Measurement of other covariates:

Physical examinations and questionnaires were administered in a similar way at baseline and follow up. Blood pressure was measured twice on the right arm in sitting position, by means of a random zero sphygmomanometer. The average of these two measurements was used. Hypertension was defined as a systolic blood pressure of ≥ 160 mm Hg and/or a diastolic blood pressure of ≥ 95 mm Hg or the self reported use of blood pressure lowering drugs. The ankle-to-brachial index was used as an indicator of atherosclerosis and was assessed by taking the ratio of the systolic blood pressure measured at the tibial artery to the systolic blood pressure measured at the right arm with a random zero sphygmomanometer, in sitting position. Blood pressure in the tibial artery was measured with a 8 MHz continuous wave Doppler probe and a random zero sphygmomanometer, in supine position (Huntleigh 500D, Huntleigh Technology, Bedfordshire, UK). Subjects with an ankle-to-brachial index less than 0.9 were considered to suffer from peripheral arterial disease.[24,25]

MRI Scanning protocol

In all participants an axial T1, T2 and PD weighted cerebral MRI scan was made on a 1.5T MRI scan. Subjects recruited from the Zoetermeer Study were scanned with a 1.5T MR Gyroscan (Philips, Best, The Netherlands) and participants from the Rotterdam Study were scanned with a 1.5T MR Vision (Siemens, Erlangen, Germany). In order to provide comparability the following pulse sequences were applied: at 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 at the Vision T1 (TR 485 ms, TE 14 ms), T2 (TR 2236, TE 90 ms) and PD (TR 2236 ms, TE 20 ms). Slice thickness was 6 mm and 5 mm respectively, with an inter-slice gap of 20.0%. The images were printed on hard copy with a reduction factor of 2.7.

White matter lesions rating scale

White matter lesions were considered present if areas were hyperintense on both PD and T2 weighted images and not hypointense on the T1 weighted image. White matter lesions were distinguished into the subcortical and periventricular region. The number and size of subcortical white matter lesions was rated on hard copy according to their largest diameter in categories of small (<3 mm), medium (3-10 mm) or large lesions (>10

mm). In order to calculate the volume of subcortical white matter lesions the lesions on hard copy were considered to be spherical with a fixed diameter per size category. Periventricular white matter lesions were rated semi-quantitatively per region (frontal, lateral or occipital) on a scale of 0 (no white matter lesions), 1 (pencil-thin periventricular lining), 2 (smooth halo or thick lining) and 3 (large confluent periventricular white matter lesions). The overall degree of periventricular white matter lesions was calculated by adding up the scores for the three separate categories (range 0-9).

Two raters from a pool of four experienced raters examined all MRI scans. In case of a disagreement of more than one point, a consensus reading was held; in all other cases the readings of both readers were averaged. The inter- and intra-rater studies showed a good to excellent agreement. Weighted kappas for grading the periventricular white matter were between 0.79-0.90. For total subcortical white matter volume the inter-reader and intra-rater intraclass correlation coefficient was 0.88 and 0.95, respectively. In addition, all MRI scans were evaluated for the presence of infarcts.

Statistical analysis

The relation between atrial fibrillation and white matter lesions was assessed with age and sex adjusted logistic regression with the presence of severe white matter lesions as the dependent variable. The associations were expressed as the relative risk (RR), as estimated by the odds ratio, with a 95% confidence interval (95% CI). White matter lesions were dichotomized at the upper quintile, which reflects severe white matter lesions. Additional adjustments were made for possible confounding factors, including hypertension, atherosclerosis (as measured by the ankle-to-brachial index) and previous myocardial infarction (based on ECG). Firstly, the analyses were performed within the whole study population. Secondly, analyses were performed in subjects with and without a stroke, defined by evidence of an infarct on the MRI scan.

It has been suggested that subjects with both atrial fibrillation and impaired left ventricular function have a more severe reduction in cardiac output, and are at a higher risk for cerebral blood flow disturbances than those with atrial fibrillation alone.[11,26] We therefore investigated the association with white matter lesions first in subjects without atrial fibrillation or left ventricular hypertrophy (reference), and compared these with subjects who had atrial fibrillation without left ventricular hypertrophy, with subjects without atrial fibrillation but with left ventricular hypertrophy

and also with subjects who had both atrial fibrillation and left ventricular hypertrophy, by creating dummy variables for the three index groups.

In 558 subjects originating from the Rotterdam Study baseline ECGs were available. This enabled us to investigate the association between white matter lesions and atrial fibrillation for only a single examination and for prolonged atrial fibrillation. We hypothesized that subjects with atrial fibrillation at both examinations would be at higher risk for having white matter lesions than subjects without atrial fibrillation or subjects with atrial fibrillation at only a single examination.

Table 1
Characteristics of the total study population of the Rotterdam Scan Study.*

	ECG available	ECG missing
Number of subjects	960	124
Age at follow up		
60-75 years	607	77
75-90 years	353	47
Age (years)	72.2 (7.5)	72.6 (7.4)
Women (%)	52.1	48.4
Total periventricular white matter lesions (grade)	2.6	2.4
Total volume subcortical white lesions (ml.)	1.6	1.3
Hypertension (%)	51.5	50.5
Peripheral atherosclerosis (%)	15.8	22.2
Atrial fibrillation (%)	3.2	n.a.
Myocardial infarction (%)	10.3	n.a.
Left ventricular hypertrophy (%)	2.9	n.a.

* values are unadjusted means (SD) or percentages.
n.a.: not available

Table 2
The relation between atrial fibrillation and presence of severe cerebral white matter lesions (RR and 95%CI).*

	Relative risk of white matter lesions (95% CI)	
	periventricular†	subcortical†
overall	2.5 (1.1-5.6)	1.3 (0.6-3.1)
< 75 years	1.6 (0.3-7.9)	0.5 (0.1-4.3)
≥ 75 years	3.2 (1.1-9.0)	1.9 (0.7-5.0)

* adjusted for age, sex, myocardial infarction, hypertension and peripheral atherosclerosis.
† dichotomized at the upper quintile of the severity distribution of white matter lesions, participants in the lower four quintiles are the reference group.

Results

Table 1 presents characteristics of the study population. Mean age of the participants was 72.2 years (SD 7.5) and 52% of them was female. The prevalence of atrial fibrillation was 1.9% among subjects below 75 years of age and 5.5% in subjects of 75 years or over. There was no significant difference between subjects with or without an ECG according to either type white matter lesions or age.

Of all participants 21% and 8% were without any periventricular or subcortical white matter lesions, respectively. Both the volume of subcortical white matter lesions and the mean grade of periventricular white matter lesions increased significantly with age.

Table 2 shows the cross-sectional association between atrial fibrillation and white matter lesions. Persons with atrial fibrillation more often had severe periventricular white matter lesions (RR 2.5; 95%CI 1.1-5.6), but not severe subcortical white matter lesions (RR 1.3; 95%CI 0.6-3.1). These associations were similar for men (RR for periventricular white matter lesions 2.4; 95%CI 0.8-6.8; and RR for subcortical white matter lesions 1.4; 95%CI 0.5-4.1) and women (RR 2.8; 95%CI 0.7-10.6 and RR 1.4; 95%CI 0.4-5.7). The associations were more marked in subjects of 75 years or over than in subjects below the age of 75 years. Of 30 subjects with atrial fibrillation 7 had a cerebral infarct on MRI scan, against 111 of 930 subjects without atrial fibrillation. The association between atrial fibrillation and white matter lesions was of the same magnitude in subjects with or without a visible infarct on the MRI scan.

The relative risks for periventricular white matter lesions for subjects with atrial fibrillation and no left ventricular hypertrophy (n=26) and for those with both atrial fibrillation and left ventricular hypertrophy (n=4), compared to the reference group, were 2.1 (95%CI 0.9-5.0) and 6.8 (95%CI 0.6-75.8), respectively. For subcortical white matter lesions no such associations were observed. There was no significant association between white matter lesions and left ventricular hypertrophy among subjects without atrial fibrillation (n=22).

Table 3 presents the associations in the part of the cohort on which baseline ECGs were available, for subjects with atrial fibrillation at both baseline and follow up examination and at only a single examination. There were 2 subjects with atrial fibrillation at baseline, but not at follow up, 8 persons without atrial fibrillation at baseline, but with atrial fibrillation at follow up, and 8 subjects with atrial fibrillation on both occasions. Subjects with atrial fibrillation detected at only one examination still had significantly more often severe periventricular white matter le-

Table 3
Relation between atrial fibrillation and severe cerebral white matter lesions for persons who had atrial fibrillation at one examination (baseline or follow-up) or at two examinations (baseline and follow-up) compared to individuals without atrial fibrillation (RR and 95%CI).*

Severe white matter lesions†	Atrial fibrillation		
	absent‡	at one examination	at both examinations
Periventricular	1.0‡	2.5 (1.1-5.6)	7.0 (1.3-39.6)
Subcortical	1.0‡	2.0 (0.5-8.0)	0.8 (0.2-3.9)

* Adjusted for age, sex, myocardial infarction, hypertension and peripheral atherosclerosis.
† Dichotomized at the upper quintile of the severity distribution of white matter lesions
‡ Reference group.

sions than those without atrial fibrillation (RR 2.5; 95%CI 1.1-5.6), but not subcortical white matter lesions (RR 2.0; 95%CI 0.5-8.0). Among subjects with atrial fibrillation at both baseline and follow-up examination the risk of severe periventricular white matter lesions was even higher (RR 7.0; 95%CI 1.3-39.6); this was again not found for subcortical white matter lesions (RR 0.8; 95%CI 0.2-3.9).

Discussion

We found an association between atrial fibrillation and periventricular white matter lesions in the cross-sectional part of our study. In addition, subjects who had atrial fibrillation at two examinations almost 5 years apart showed an even higher prevalence of periventricular white matter lesions. Subjects with atrial fibrillation and concomitant left ventricular hypertrophy were at the highest risk of having periventricular white matter lesions. These associations were not found for subcortical white matter lesions. The strength of this study is its large number of elderly people from the general population, including institutionalized persons. Another important feature is the availability of an ECG recorded 5 years before MRI scanning, in part of our population.

The overall response rate was 63%, which raises the question of selection bias. Since non-responders were older than responders, it is likely that non-responders have higher degrees of white matter lesions. However, we could not think of any reason why the association between atrial fibrillation and presence of white matter lesions would be different in non-

responders than in responders, but we can of course not fully rule out that selection bias may have played a part in our findings.

About 11% of all subjects with an MRI scan were excluded from the analyses because of a missing ECG. Selection bias might have occurred if participation in the ECG measurement were related to the presence of white matter lesions. However, in our study missing ECGs were mostly explained by technical problems of the ECG recorder. Also, the severity of white matter lesions was similar in subjects with or without an ECG. We therefore consider it unlikely that missing ECG measurements are related to white matter lesions.

We probably underdiagnosed the prevalence of atrial fibrillation, since we only used one 10 second resting ECG for the detection of rhythm disturbances. We therefore could not detect all episodes of paroxysmal atrial fibrillation. Findings by Manolio et al. indicated that 74% of all patients with atrial fibrillation identified during a 24-hour ambulatory ECG assessment were detected with a 10 second ECG recording.[27] Since this misclassification is most likely not related to presence of white matter lesions and is therefore non-differential, it will have reduced the strength of the association between atrial fibrillation and white matter lesions towards the null hypothesis.

The association between atrial fibrillation and periventricular white matter lesions might be confounded by the underlying cause of atrial fibrillation, including ischemic heart disease, atherosclerosis and hypertension.[26,28] However, adjustments for these variables did not alter the strength of the association between atrial fibrillation and white matter lesions, which suggests a direct effect of atrial fibrillation on the periventricular white matter.

There are two possible ways in which atrial fibrillation may result in the emergence of white matter lesions. The first is a reduction of cerebral perfusion by a reduced cardiac output in patients with atrial fibrillation, especially at a fast ventricular rate (i.e. during periods of increased activity).[26] Especially among elderly people, who may already have a compromised cerebral circulation, atrial fibrillation further reduces brain perfusion.[26,29,30] A chronic reduction in cerebral blood flow might lead to ischemia of the white matter, reflected in white matter lesions, especially in the presence of the compromised cerebral circulation in the aging brain. This hemodynamic contribution to the pathogenesis of periventricular white matter lesions is further supported by our finding of an even stronger association between atrial fibrillation and periventricular white matter lesions in the subgroup of subjects with impaired left ventricular function. This is a group of subjects with an even greater reduction of

cardiac output and cerebral perfusion than subjects with atrial fibrillation alone.[11,26]

The second possible explanation is that atrial fibrillation leads to the formation of intracardiac thrombus, which may result in arterial thrombo-embolism.[26] Such thrombi might occlude large or small arteries in the brain, resulting in overt stroke[28] or in micro-infarction of brain tissue, including the white matter. If this explanation were involved in the pathogenesis of white matter lesions one would expect a stronger association between atrial fibrillation and white matter lesions among subjects with evidence of infarction than in those without. As we found no difference in this respect between subjects with or without recognizable infarcts, this suggests that thrombo-embolism is not an important factor in the development of white matter lesions in subjects with atrial fibrillation. Yet, cautious interpretation of these data is necessary since there were only 7 cases with both atrial fibrillation and a visible infarct on MRI scanning.

Like others we have found that atrial fibrillation was associated especially with periventricular white matter lesions, whereas this was less clear for the subcortical region.[17] This suggests that different pathophysiological factors may underlie periventricular and subcortical white matter lesions. The periventricular white matter is an arterial border zone, already marginally perfused under physiological circumstances, which makes it especially vulnerable by a decrease of cerebral blood flow.[9,16,31] In contrast, the subcortical white matter is not an arterial watershed area.[32] We found an association between atrial fibrillation and periventricular white matter lesions. Others have found an association between atrial fibrillation and dementia and cognitive impairment,[13,14] while the association between white matter lesions and dementia is well established.[5,33,34] Effective treatment of atrial fibrillation is available and may prevent or reduce the development of white matter lesions and of the concomitant decline in cognitive performance, especially in the elderly.

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4.4 Cerebral vasomotor reactivity and cerebral white matter lesions

Abstract

Objective *The pathogenesis of white matter lesions is still uncertain but an ischemic-hypoxic cause has been suggested. Cerebral vasomotor reactivity reflects the compensatory dilatory mechanism of the intracerebral arterioles to a vasodilatory stimulus and provides a more sensitive hemodynamic index than the level of resting flow.*

Methods *We determined the association between vasomotor reactivity and white matter lesions in 73 consecutive individuals from the Rotterdam Scan Study who also participated in the Rotterdam Study, a large population based prospective follow-up study of individuals aged 55 years and over. Vasomotor reactivity was measured by means of CO_2-enhanced transcranial Doppler and in all individuals axial T_1, T_2 and PD weighted MRI scans (1.5T) were obtained. White matter lesions were scored according to location, size and number by two independent readers.*

Results *Vasomotor reactivity was inversely associated with the presence of deep subcortical and total periventricular white matter lesions (OR 0.5; 95%CI 0.3-1.1 and OR 0.7; 95%CI 0.4-1.1, respectively). A strong association was found between impaired vasomotor reactivity and periventricular white matter lesions adjacent to the lateral ventricular wall (OR 0.6; 95%CI 0.4-1.0;* p *=0.001). No*

association was found with periventricular white matter lesions near the frontal and occipital horns.

Conclusions *Our data confirm the association between vasomotor reactivity and white matter lesions and support the hypothesis that some white matter lesions may be associated with hemodynamic ischemic injury to the brain.*

Introduction

White matter lesions are frequently detected on magnetic resonance imaging (MRI) in the elderly and the extent of these white matter lesions correlates positively with age[1,2] and several cerebrovascular risk factors.[3,4] The pathogenesis of these white matter lesions is still largely unknown[5,6] but a hemodynamic contribution has been suggested.[7-10] Cerebral vasomotor reactivity, or cerebrovascular reserve capacity, reflects the compensatory dilatory mechanism to a vasodilatory stimulus of the intracerebral arterioles,[11] and provides a more sensitive hemodynamic index than the level of resting blood flow.[12] The vasomotor reactivity can be estimated by means of CO_2-enhanced transcranial Doppler and has become a well established method for evaluating possible hemodynamic failure for instance in occlusive carotid artery disease.[13-18]

The association between vasomotor reactivity and white matter lesions has never been examined in a population based study among elderly individuals. In series of asymptomatic individuals and individuals with hypertension a decreased vasomotor reactivity has been found to be associated with periventricular lesions on MRI.[19,20] There are no reports on the relationship between vasomotor reactivity and subcortical white matter lesions.

We investigated the association between vasomotor reactivity and different subtypes of white matter lesions in 73 individuals selected from a population-based study.

Methods

For the current study eighty individuals were randomly selected from the Rotterdam Scan Study. The Rotterdam Scan Study is a population-based study of causes and consequences of brain changes as visible on MRI. Persons with dementia and contraindications for MRI were excluded. This study was carried out between July and September 1996 and based on

the part of the cohort that also participated in the Rotterdam Study, which focuses on determinants of neurological, cardiovascular, endocrinal and ophthalmologic diseases in the elderly.[21]

Transcranial Doppler monitoring was performed (Multi-Dop X-4, DWL, Germany) and mean cerebral blood flow velocity was continuously measured in the middle cerebral artery on both sides if possible, as follows. The subject breathed air and 5% carbon dioxide through an anaesthetic mask, tightly fit over mouth and nose. End-tidal CO_2 pressure (mmHg) was recorded continuously with a CO_2 analyzer (Multinex, Datascope). Individuals first breathed room air, until a steady expiratory end-tidal CO_2 was obtained. Individuals were then asked to inhale a mixture of 5% carbon dioxide in 95% oxygen for 2 minutes and the end-tidal CO_2 was recorded. End-expiratory CO_2 was assumed to reflect arterial CO_2.[11] TCD-8 DWL special software (VMR-CO_2) was used. All transcranial Doppler data were stored on hard disk for off-line analysis. Vasomotor reactivity was defined as the percentage increase in blood flow velocity occurring during inspiration of 5% CO_2, divided by the absolute increase in end-tidal CO_2 in the same time period (%/mmHg). The mean of the right and left vasomotor reactivity was used for the analyses if both middle cerebral arteries could be insonated adequately. The one-sided vasomotor reactivity was used if a window-failure appeared on one side.

Each subject underwent cerebral MRI scanning using a 1.5 Tesla (T) Siemens Gyroscan. From each participant axial T_1 (TR 700ms, TE 14ms), T_2 (TR 2200, TE 80ms) and proton density (PD) (TR 2200, TE 20ms) weighted images were made. Slice thickness was 5mm, with a gap of 1.0mm. All MRI scans were examined independently by two experienced readers. White matter lesions were considered present if visible on both PD and T_2 weighted images and not on the T_1 weighted image. White matter lesions were distinguished into the deep subcortical and those in the periventricular region (Figure 1). The number of deep subcortical white matter lesions was counted on hard copy according to their largest diameter in categories of small (<3 mm), medium (3-10 mm) or large lesions (>10 mm). In order to calculate a deep subcortical white matter lesions volume, the white matter lesions were considered to be spherical with a fixed diameter per size category. Periventricular white matter lesions were scored semi-quantitatively per region (adjacent to the frontal horn or frontal capping, adjacent to the lateral wall of the lateral ventricles or bands and adjacent to the occipital horn or occipital capping) at a scale ranging from 0 (no white matter lesions), 1 (pencil-thin periventricular lining), 2 (smooth halo or thick lining) to 3 (large confluent white matter lesions). Total severity of periventricular white matter lesions was calculated by adding up the scores of the three separate categories

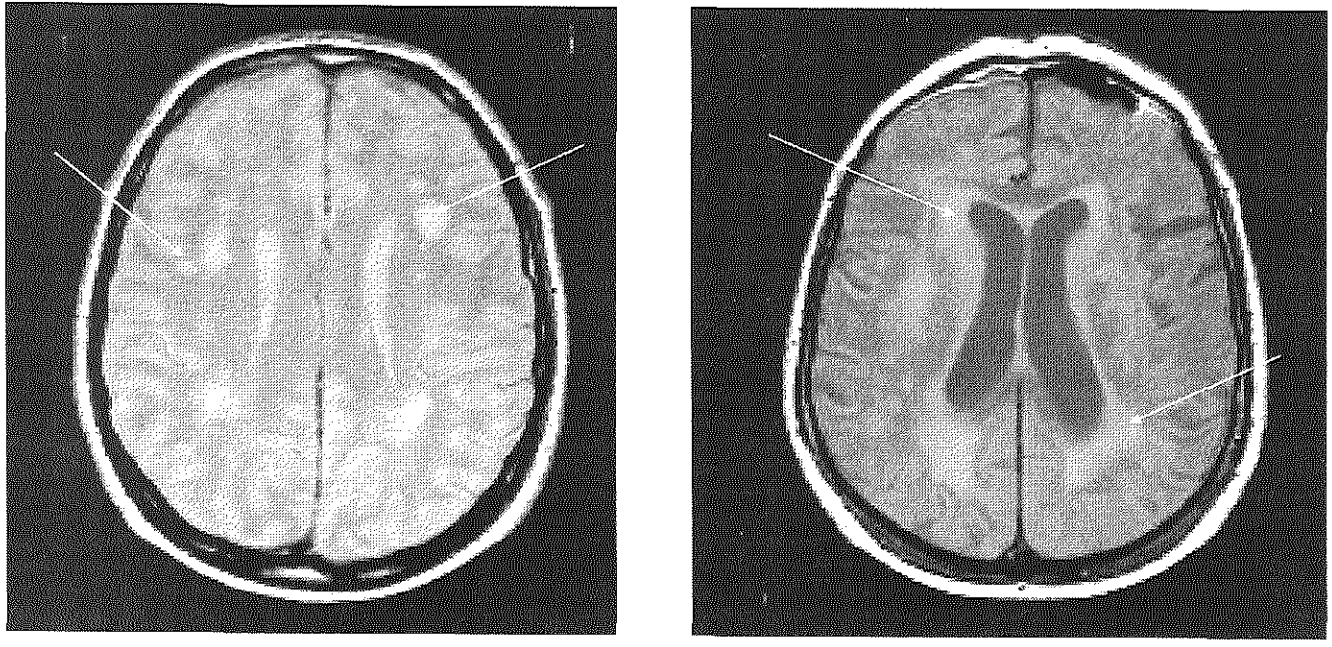


Figure 1
Arrows in the left panel indicate deep subcortical white matter lesions, whereas arrows in the right panel indicate periventricular white matter lesions.

(range 0-9). All MRI scans were examined by two raters from a pool of four experienced raters. In case of a disagreement of more than one point, a consensus reading was held; in all other cases the average of the two readers was calculated. Inter- and intra-rater studies showed a good to excellent agreement. Weighted kappas were calculated with respect to scoring of the periventricular white matter lesions (weighted kappa between 0.79-0.90). Intraclass correlation coefficients were calculated for deep subcortical white matter lesions (r^2 = 0.88 for total volume of deep subcortical white matter lesions).

To assess the relationship between vasomotor reactivity and presence of white matter lesions, age and sex adjusted logistic regression was used. In these analyses vasomotor reactivity was used as a continuous variable and white matter lesions were dichotomized at the upper quintile. All analyses were performed using BMDP statistical software.[22] To detect a possible threshold, the association between tertiles of vasomotor reactivity and extent of white matter lesions was assessed using age and sex adjusted linear regression.

Results

Combined TCD and MRI data were obtained in 73 individuals (91%). The other individuals had either window failure on both sides (n=4) or dif-

Table 1
Baseline characteristics from the study population and The Rotterdam Study.

	Study population N=73	Rotterdam Study N=7123	*p* value
Age (years)	70.2 (8.0)	72.8 (8.0)	0.003*
Sex (men)	74	41	<0.0001*
Ankle-brachial-index	1.2 (0.02)	1.1 (0.003)	NS
Systolic blood pressure (mmHg)	138 (21.5)	139 (21.4)	NS
Diastolic blood pressure (mmHg)	74 (11.5)	74 (11.5)	NS
Hypertension	41	45	NS
Diabetes	5	8	NS
History of myocardial infarct	12	11	NS
History of stroke	3	3	NS
History of peripheral arterial disease†	7	11	NS

Values represent means (SD) or percentages
NS = non significant
* *p* value was calculated performing analysis of co-variance
† Peripheral arterial disease was defined as ankle-brachial-index < 0.9

ficulties wearing the dose-fitting mask (n=3). MRI examination was tolerated well. Mean age of the study population was 70.2 years and 74% of all individuals were men. Except for age and sex, vascular risk factors were equally frequent in The Rotterdam Scan study as in The Rotterdam Study as a whole (Table 1). Mean vasomotor reactivity was 3.4 %/mmHg and ranged from 0.8-6.3%/mmHg with a normal distribution. A correlation coefficient of 0.94 was found between right and left vasomotor reactivity. Women tended to have a lower vasomotor reactivity than men: mean 3.0 versus 3.6%/mmHg (p=0.4). Sixty-eight percent of the individuals had at least some periventricular white matter lesions and 86% at least some deep subcortical white matter lesions. Fifty-seven percent of the individuals had periventricular white matter lesions adjacent to the lateral ventricular wall (bands).

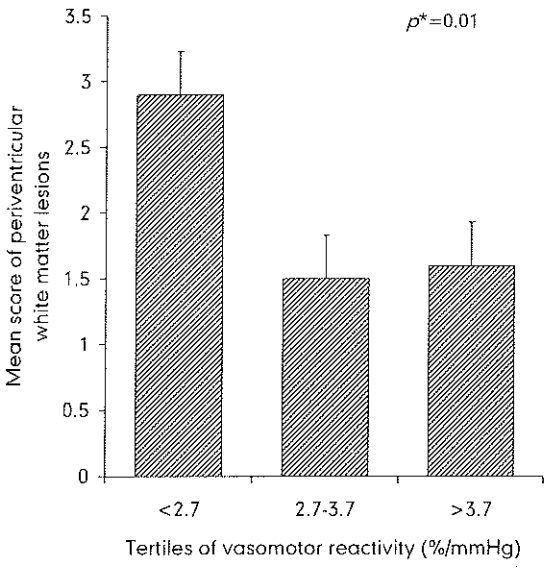
Vasomotor reactivity was inversely associated with severe deep subcortical and total periventricular white matter lesions (OR 0.5; 95%CI 0.3-1.1 and OR 0.7; 95%CI 0.4-1.1 per 10% vasomotor reactivity, respectively). Figure 2 shows that individuals with higher vasomotor reactivity had a significantly lower mean score of total periventricular white matter lesions (p=0.01). As shown in Figure 3, individuals with higher vasomotor reactivity had also a significantly lower mean score of total deep subcortical white matter lesions volume (p=0.02).

Table 2 gives the mean score of white matter lesions in each periventricular region per tertile of vasomotor reactivity and provides the mean scores for deep subcortical white matter lesions for each size in the different vasomotor reactivity groups. Individuals in the lowest tertile of vasomotor reactivity were found to have the highest mean score of white matter lesions in all three periventricular regions, whereas individuals in

Table 2
The association between cerebral vasomotor reactivity (VMR [%/mmHg]) and white matter lesions (WML) per region (periventricular) and per size (deep subcortical).*

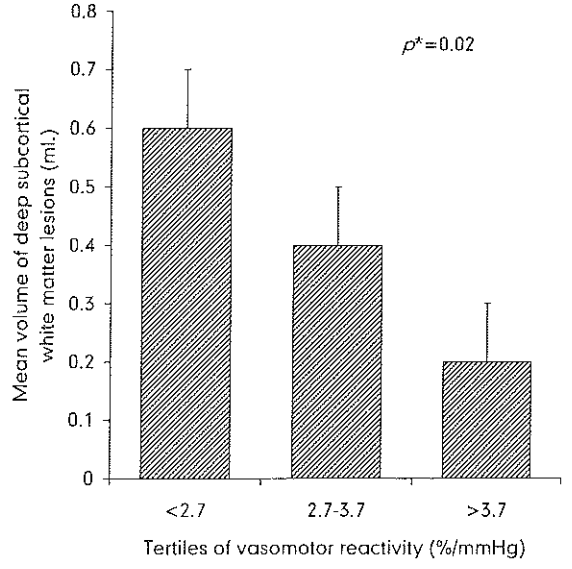
	VMR<2.7	VMR 2.7-3.7	VMR>3.7	p†
frontal capping	0.9 (0.13)	0.4 (0.13)	0.6 (0.13)	0.06
occipital capping	0.8 (0.14)	0.5 (0.14)	0.4 (0.14)	0.13
bands	1.2 (0.13)	0.6 (0.13)	0.6 (0.13)	0.001
large deep subcortical WML	1.2 (0.3)	0.5 (0.3)	0.2 (0.3)	0.02
medium deep subcortical WML	0.3 (0.08)	0.3 (0.08)	0.2 (0.08)	0.20
small deep subcortical WML	0.1 (0.02)	0.06 (0.02)	0.06 (0.02)	0.03

* Values represent mean score (SE) of periventricular and mean volume (SE) [ml.] of deep subcortical white matter lesions and are adjusted for age and sex.
† p values were calculated in a test for trend.



* p value was calculated in a test for trend

Figure 2
The association between tertiles of cerebral vasomotor reactivity (%/mmHg) and mean total score (SE) of periventricular white matter lesions, adjusted for age and sex.



* p value was calculated in a test for trend

Figure 3
The association between tertiles of cerebral vasomotor reactivity (%/mmHg) and mean volume (SE) of total deep subcortical white matter lesions (ml.), adjusted for age and sex.

the highest tertile of vasomotor reactivity had the lowest mean score. The inverse association between vasomotor reactivity and white matter lesions seemed strongest with periventricular white matter lesions adjacent to the lateral ventricular wall (p=0.001). Better vasomotor reactivity was associated with less deep subcortical lesions, irrespective of the size of the lesions.

Discussion

This is the first study to show an association between vasomotor reactivity, assessed by means of CO_2-enhanced transcranial Doppler, and the presence and extent of white matter lesions in a population based study among elderly individuals. The results suggest that vasomotor reactivity is inversely associated with white matter lesions in the periventricular as well as in the deep subcortical regions. A strong association was found between impaired vasomotor reactivity and periventricular white matter lesions adjacent to the lateral ventricular wall (bands) in particular.

There are few reports on the relationship between magnetic resonance white matter lesions, cerebral blood flow and the subject's ability to increase cerebral blood flow in response to hypercapnia. Most investigators have found no significant changes in resting cerebral blood flow in individuals with asymptomatic periventricular white matter lesions,[23,24] although one study with positron emission tomography showed that in such patients cerebral blood flow was low compared to the oxygen requirements of the (surrounding) healthy brain.[25] Others have found decreased cerebral blood flow values in areas of white matter lesions compared to areas with normal white matter.[23,25-27] For the detection of reductions in cerebral perfusion, measurements of resting cerebral blood flow alone may be insufficient. Cerebral perfusion may only be impaired in situations where there is increasing demand, due to failure of normal compensatory mechanisms. This can be estimated by the determination of vasomotor reactivity that provides a more sensitive hemodynamic index than the level of resting blood flow.[12]

In one study with asymptomatic individuals, the severity of periventricular white matter lesions was significantly and negatively correlated with a decrease in vasomotor reactivity and not with resting cerebral blood flow, which led the authors to suggest that the reduction of vasomotor reactivity is a more important hemodynamic marker in the pathogenesis of periventricular white matter lesions than is a decrease in the level of resting blood flow.[19] This inverse association between a decrease in vasomotor reactivity and the severity of white matter lesions was subsequently found in hypertensive patients with leukoaraiosis.[20]

In our study, we found an increased mean score of periventricular white matter lesions, as well as an increase in severe deep subcortical white matter lesions volume in individuals with the lowest vasomotor reactivity scores. A strong and inverse association was found between low vasomotor reactivity and bands which suggests that periventricular

regions adjacent to the lateral ventricle wall harbor a circulatory borderzone and may have less microcirculatory anastomoses than the other periventricular zones. The relationship between cerebral hemodynamics and white matter lesions has not been fully explored. Hypoxia-ischemia, disturbances in the circulation of the cerebrospinal fluid and changes in the permeability of the blood brain barrier to macromolecules are thought to play an important role in the pathogenesis of white matter lesions.[7] Several arguments support the hypothesis that some types of white matter lesions may be the result of ischemic injury to the brain.[7-10] The region of the white matter immediately adjacent to the lateral ventricular walls receives its blood supply from the ventriculofugal vessels arising from the subependymal arteries, which originate either from the choroidal arteries or from terminal branches from the lenticulostriatal arteries.[7,25] Anastomoses between the vessels originating at the surface as well as those branching off the subependymal system are either scarce or absent, leading to a minimal overlap between the territories of the different end arteries.[28-31] This pattern of vascularization suggests that the periventricular white matter harbors an arterial borderzone, particularly susceptible to injury from systemic or focal decreases in cerebral blood flow,[7,32] although this has been challenged by others.[33-35] Hypoperfusion can result either from arteriolosclerotic changes affecting the small intraparenchymal arteries and arterioles that are associated with aging and with stroke risk factors,[7,32,36,37] or by hemodynamic mechanisms in case these arteries are already maximally dilated, for instance in high grade carotid artery stenosis or occlusion, in which cerebral perfusion can become directly dependent of the systemic arterial blood pressure. This may explain the inability to increase focal blood flow in response to hypercapnia in these individuals. In the former, a drop in blood-pressure may result in hypoperfusion and ischemic changes to the deep white matter. It is very unlikely that high grade internal carotid artery stenosis contributes to our findings. Data on the prevalence of significant stenosis or occlusion of the carotid artery in a non-hospitalized elderly population are limited, but results from the Rotterdam Study show a prevalence of about 0.5-1.0%.[38] We therefore consider it unlikely that this will affect the association we found. An association between white matter lesions and atherosclerotic abnormalities in the carotid artery, the coronary arteries and in the peripheral vessels has already been established.[39] It is still unclear however, how different types of ischemia may induce selected structural changes of the white matter. We did not determine systemic blood pressure. Although systolic and diastolic blood pressure rise during a

period of hypercapnia, it is still unclear whether and how this affects flow velocity in the cerebral arteries.

Future studies should elucidate the clinical and pathogenetic relevance of vasomotor reactivity in individuals with white matter lesions.

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Chapter 5

Apolipoprotein E genotype and cerebral white matter lesions

5 Apolipoprotein E genotype and cerebral white matter lesions

Abstract

Background *Cerebral white matter lesions are frequently observed on cerebral MRI scans of both non-demented and demented elderly people. Cardiovascular risk factors are major determinants of these lesions. They have been associated with cognitive impairment. Few studies investigated the relations between white matter lesions and the different APOE genotypes. A 1.5 times increase in risk for white matter lesions among APOE*4 carriers has been reported, but other results are inconsistent. As the presence of this allele increases the risk for cognitive decline and dementia, especially in the presence of atherosclerosis, white matter lesions might be intermediate factors in this association. We studied the association between the APOE genotype and white matter lesions.*

Methods *In 1995-1996 we randomly sampled 568 subjects, aged 60-90 years, from the Rotterdam Study. In 545 participants APOE genotyping was done, all of whom also subjects underwent 1.5T MRI-scanning; white matter lesions were rated for the periventricular and subcortical regions separately.*

Results *Subjects with the APOE2E4 genotype had the highest volume of subcortical white matter lesions and the highest mean grade of periventricular white matter lesions (2.6 ml; SE 0.9 and 4.1; SE 0.6, respectively). For subjects with an APOE*4 allele compared to the APOE3E3 carriers these figures were 2.2 ml. (SE 0.2)* versus *1.6 ml. (SE 0.2); p <0.05), and 2.9 (SE 0.2) versus 2.7 (SE 0.2);*

*p=0.26), respectively. Subjects with the APOE2E4 genotype had twice as often severe subcortical white matter lesions and almost seven times as often severe periventricular white matter lesions as subjects with the APOE3E3 genotype (RR 2.0; 95%CI 0.5-8.7 and RR 6.8; 95% 1.8-25.5, respectively). Participants with an APOE*4 allele had a borderline significantly increased risk for having severe subcortical as well as periventricular white matter lesions (RR 1.5, 95%CI 0.9-2.5 and RR 1.5, 95%CI 0.9-2.5, respectively) compared with APOE3E3 carriers. Adjustment for vascular risk factors and atherosclerosis did hardly change the magnitude of the associations.*

Conclusion *Among carriers of the APOE*4 allele there was an increased risk for severe white matter lesions.*

Introduction

White matter lesions are a common finding on magnetic resonance imaging (MRI) scans of elderly non-demented as well as demented people.[1-3] These lesions can be distinguished in periventricular and subcortical white matter lesions, on the basis of their location. There is increasing evidence that white matter lesions play an important role in the development of cognitive decline and dementia.[3-6] To date, there is only a single study that addressed the role of the apoliprotein E genotype (APOE) on white matter lesions.[7] In addition, Schmidt et al investigated the association between the APOE genotype on the one hand and microangiopathy related cerebral damage, a plethora of brain abnormalities including white matter lesions and lacunar infarcts on the other.[8] They found that carriers of the APOE2E3 allele had more often microangiopathy related cerebral damage than APOE3E3 carriers.[8] Both studies reported a non-significant increase in risk for white matter lesions in carriers of the APOE*4 genotype.

The APOE*4 allele of the gene is associated with an increased risk of cognitive decline and dementia, in particular in the presence of atherosclerosis.[9] The factors through which the APOE*4 allele increases the risk for cognitive decline and dementia is not known, though it is suggested that cerebral white matter lesions are involved.[10]

Apolipoprotein E (ApoE) plays a crucial role in the transport of lipoproteins, but also has anti-oxidant and anti-inflammatory capacities, and is involved in neuronal outgrowth.[11-16] ApoE serum levels are fully determined by the apolipoprotein E gene (APOE), which has three alleles, APOE*2, APOE*3 and APOE*4.

Our objective was to study the role of the APOE genotype on the presence of cerebral white matter lesions in the Rotterdam Scan Study.

Methods and subjects

Study population

This study is based on the Rotterdam Scan Study, designed to study determinants and cognitive consequences of age related brain abnormalities in the elderly. The study comprises random samples of two large population based studies, the Rotterdam Study and the Zoetermeer Study. The present study deals with participants from the Rotterdam sub-population. This study has been described in detail elsewhere.[17] In short, the Rotterdam Study is a prospective population based cohort study among 7983 subjects, aged 55 years and over in which studies of neurological, ophthalmological, cardiovascular and locomotor diseases (baseline data collection 1990-1993) are performed. In 1995-1996, a sample of 837 subjects aged between 60-90 years was randomly selected in strata of age (5 years) and sex; 568 of them underwent MRI scanning as part of the Rotterdam Scan Study (response 68%). The study was approved by the medical ethics committee of the Erasmus University. Each subject signed an informed consent form.

APOE genotyping

APOE genotyping was done on coded genomic DNA samples, without knowledge of the white matter lesions rating. The apolipoprotein E gene was amplified by means of the primers and amplification conditions described by Wenham et al.[18] The results were read by three raters independently; in case of discrepancies the APOE genotyping was repeated.

Measurement of covariates

Height and weight were measured without shoes in light clothing. The body-mass-index was calculated as weight divided by height square. Blood pressure was measured two times on the right arm by means of a random zero sphygmomanometer, with the participant in sitting position. The average of these two measurements was used. As an indicator of atherosclerosis the ankle-to-brachial index was evaluated by measurement of the blood pressure of the tibial artery using a 8 MHz continuous wave Doppler probe (Huntleigh 500D, Huntleigh Technology, Bedfordshire, UK) and for the brachial artery with a random zero sphygmomanometer, the

participant being supine. The ankle-to-brachial index was defined as the systolic blood pressure measured at both the left and right posterior tibial artery divided by the systolic blood pressure of the right arm. Subjects with an ankle to brachial index below 0.9 were considered to have peripheral arterial disease.[19,20] Diabetes mellitus was considered present if the participant was taking oral anti-diabetics or insulin.

MRI Scanning protocol

In all participants an axial T1, T2 and Proton Density (PD) weighted cerebral MRI scan was made on a 1.5T MR VISION (Siemens, Erlangen, Germany). The following pulse sequences were applied at the VISION: T1 (TR 700 ms, TE 14 ms), T2 (TR 2200 ms, TE 80 ms) and PD (TR 2200 ms, TE 20 ms) Slice thickness was 5 mm with an inter-slice gap of 20.0%. The images were printed on hard copy with a reduction factor of 2.7.

White Matter Lesions Rating Scale

White matter lesions were considered present if these were hyper-intense on both PD and T2 weighted images and not hypo-intense on T1 weighted images. White matter lesions were distinguished into those in the subcortical and periventricular region. The number and size of subcortical white matter lesions was rated on hard copy according to their largest diameter in categories of small (<3 mm), medium (3-10 mm) or large lesions (>10 mm). In order to calculate the volume of subcortical white matter lesions on hard copy, they were considered to be spherical with a fixed diameter per size category. Periventricular white matter lesions were rated semi-quantitatively per region: adjacent to the frontal horns (frontal capping); adjacent to the lateral wall of lateral ventricles (bands), and adjacent to the occipital horns (occipital capping), on a scale ranging from 0 to 3. The overall degree of periventricular white matter lesions was calculated by adding up the scores for the three separate categories (range 0-9). All MRI scans were examined by two raters from a pool of four experienced raters. In case of a disagreement of more than one point, a consensus reading was held; in all other cases the readings of both readers were averaged. The inter- and intra-rater studies showed a good to excellent agreement. Weighted kappas for grading the periventricular white matter were between 0.79-0.90. For total subcortical white matter volume the inter- and intra-rater intra-class correlation coefficient was 0.88 and 0.95, respectively.

Data analysis

Mean volume of subcortical and mean grade of periventricular white matter lesions were calculated for each APOE genotype by age and sex adjusted analyses of covariance. Since there is evidence that in particular severe white matter lesions are associated with cognitive impairment we investigated the relation between the APOE gene and severe white matter lesions by means of age and sex adjusted logistic regression with the presence of severe white matter lesions as the dependent variable.[1,3] The APOE genotypes were entered in the model as dummy variables, with the APOE3E3 genotype as the reference group. White matter lesions were dichotomized at the upper quintile.

Since previous studies investigated the effect of the APOE*4 gene on white matter lesions and because of the suggested synergism between white matter lesions and APOE*4 on the occurrence of dementia the previous analyses were done again for carriers of an APOE*4 allele (APOE2E4, APOE3E4 and APOE4E4) compared to the APOE3E3 group. Participants with and APOE2E2 and APOE2E3 genotype were excluded from these analyses. To study the association between APOE and white matter lesions irrespective of possible intermediate vascular factors additional adjustments were made for systolic and diastolic blood pressure, the body-mass-index, presence of diabetes mellitus and presence of peripheral arterial disease. The association was calculated as the relative risk (RR), as estimated by the odds ratio, and was presented with a 95% confidence interval (95% CI).

Results

DNA for Apolipoprotein E genotyping was available for 545 subjects of the 568 participants. The distribution of the APOE genotype was in Hardy-Weinberg equilibrium ($\chi_{df=3}$=1.1, p=0.77).

Table 1 presents the characteristics of the study population. Mean age of the participants was 73.6 years (SD 7.9); 49% were women. These figures were similar for all APOE genotypes. Subjects with the APOE2E2 genotype (n=4) had a considerably higher prevalence of peripheral arterial disease (50.0%) than the others (about15%). With respect to the other characteristics no major differences were observed between the several APOE genotypes. Of all participants 20% were without periventricular white matter lesion and 8% without subcortical white matter lesions.

Subjects with the APOE2E4 genotype had the highest volume of subcortical white matter lesions and the highest mean grade of periventricu-

Table 1
Characteristics of the study population

Number of subjects	545
Mean age at follow-up (yrs)	73.6 (7.9)
Women (%)	49.2
Body Mass Index (kg/m^2)	26.3 (3.5)
Diabetes Mellitus (%)	6.4
Systolic BP (mm Hg)	146.2 (20.5)
Diastolic BP (mm Hg)	76.5 (11.5)
Ankle-to-brachial index	1.1 (0.2)
Peripheral arterial disease (%)†	17.3

* Values are unadjusted means (SD) or percentages.
† Defined as an ankle-to-brachial index below 0.9.

lar white matter lesions (2.6 ml; SE 0.9 and 4.1; SE 0.6, respectively; table 2) compared with the other APOE genotypes. Participants with at least one APOE*4 allele had a significantly increased volume of subcortical white matter lesions compared to the APOE3E3 carriers (2.2 ml. (SE 02) *versus* 1.6 ml. (SE 0.2); p =0.025), whereas the mean grade of periventricular white matter lesions was not significantly different for the two groups (2.9 (SE 0.2) versus 2.7 (SE 2.0); p=0.26).

Table 3 presents the associations between severe white matter lesions and each APOE genotype. Subjects with the APOE2E4 genotype had the highest risk for severe subcortical and periventricular white matter lesions (RR 2.0; 95%CI 0.5-8.7 and RR 6.8; 95% 1.8-25.5, respectively) as compared to APOE3E3 carriers. Adjustment for vascular risk factors such as systolic and diastolic blood pressure, diabetes mellitus, body-mass-index, and peripheral arterial disease, did not appreciably change the magnitude of the associations. Participants with at least one APOE*4 allele had a borderline significantly increased risk for having both severe subcortical and periventricular white matter lesions (RR 1.5; 95%CI 0.9-2.5 and RR 1.5; 95%CI 0.9-2.5, respectively).

Discussion

We found that individuals with the APOE2E4 genotype had, on average, more subcortical and periventricular white matter lesions than subjects with other APOE genotypes. In addition they were at the highest risk for severe subcortical as well as severe periventricular white matter lesions. Carriers of at least one APOE*4 gene had a significantly higher volumes of subcortical white matter lesions and a borderline significantly increased risk for both types of severe white matter lesions.

Table 2
The relation between the APOE genotype and the mean volume of cerebral white matter lesions.

Apolipoprotein E	E2E2 (n=4)	E2E3 (n=60)	E2E4 (n=12)	E3E3 (n=321)	E3E4 (n=137)	E4E4 (n=11)	E4+ (n=160)
Subcortical white matter lesions*							
Adjusted for age and sex	1.2 (1.5)	1.9 (0.4)	2.6 (0.9)	1.6 (0.2)	2.2 (0.3)	1.2 (0.9)	2.2 (0.2)‡
Adjusted for age, sex and vascular risk factors†	0.4 (1.7)	1.8 (0.4)	2.3 (0.9)	1.4 (0.2)	2.1 (0.3)	1.1 (0.9)	2.1 (0.2)‡
Periventricular white matter lesions*							
Adjusted for age and sex	2.3 (1.0)	3.0 (0.3)	4.1 (0.6)	2.7 (0.1)	2.8 (0.2)	2.6 (0.6)	2.9 (0.2)
Adjusted for age, sex and vascular risk factors†	1.6 (1.1)	2.9 (0.3)	3.9 (0.6)	2.6 (0.1)	2.7 (0.2)	2.5 (0.6)	2.8 (0.2)

* Values represent mean volume for subcortical lesions or the mean grade for periventricular lesions and the standard error.
† Vascular factors including systolic and diastolic blood pressure, body-mass-index, diabetes mellitus and presence of peripheral arterial disease.
‡ $p < 0.05$, with APOE3E3 as the reference group.

Table 3
The relation between the APOE genotype and the presence of severe cerebral white matter lesions (RR and 95% CI).

Apolipoprotein E	E2E2 (n=4)	E2E3 (n=60)	E2E4 (n=12)	E3E3 (n=321)	E3E4 (n=137)	E4E4 (n=11)	E4+ (n=160)
Subcortical white matter lesions*							
Adjusted for age and sex	1.0 (0.1-10.8)	1.4 (0.7-2.9)	2.0 (0.5-8.7)	1.0 (ref)	1.5 (0.9-2.6)	1.4 (0.3-7.0)	1.5 (0.9-2.5)
Adjusted for age, sex and vascular risk factors†	‡	1.4 (0.7-2.9)	1.7 (0.4-7.5)	1.0 (ref)	1.5 (0.9-2.6)	1.0 (0.1-8.4)	1.5 (0.9-2.5)
Periventricular white matter lesions*							
Adjusted for age and sex	0.8 (0.1-8.8)	1.1 (0.5-2.3)	6.8 (1.8-25.5)	1.0 (ref)	1.3 (0.7-2.1)	2.1 (0.5-9.2)	1.5 (0.9-2.5)
Adjusted for age, sex and vascular risk factors†	‡	1.2 (0.6-2.5)	6.6 (1.7-24.8)	1.0 (ref)	1.3 (0.8-2.2)	2.0 (0.4-10.3)	1.4 (0.9-2.4)

* Dichotomized at the upper quintile of the severity distribution of white matter lesions.
† Vascular factors including systolic and diastolic blood pressure, body-mass-index, diabetes mellitus and presence of peripheral arterial disease.
‡ Not calculated due to small numbers.

Some methodological issues need to be considered. Our study was population based, but some selection bias may have occurred due to non-response. Most likely, the participation rate was lowest among subjects with the highest degree of white matter lesions. Besides this, since participants with an APOE*4 allele convey the highest risk for dementia and since only non-demented persons were included in the study, APOE*4 carriers may have been underrepresented. Another potential source of bias is survival bias, but recent findings from the Rotterdam Study suggested that survival is not different across APOE genotypes.[21] In addition, the distribution of the APOE genotype was in Hardy-Weinberg equilibrium in our population. Therefore we consider it unlikely that either selection bias or survival bias has influenced our findings.

It may be that atherosclerosis is an intermediate factor in the association between the APOE genotype and white matter lesions. That is, APOE might be a determinant of atherosclerosis, and atherosclerosis in turn might be a determinant of white matter lesions. However, recent studies found no association between the APOE*4 allele and atherosclerosis,[22] whereas the association between indicators of atherosclerosis and white matter lesions is well established.[1,23] Indeed, in our analysis adjusting for atherosclerosis and other vascular factors did not change the magnitude of the association between APOE*4 and white matter lesions, suggesting that atherosclerosis is not an intermediate factor in this association.

Schmidt et al. reported an odds ratio of 3.0 for the association between carriers of the APOE2E3 allele and microangiopathy related cerebral damage. We can not confirm this association in our study. However, a difficulty in comparing the findings of Schmidt et al with our findings is that their definition microangiopathy-related cerebral damage included not only white matter lesions but also lacunar infarcts. Among individuals with the APOE2E4 genotype we found twice as often severe subcortical white matter lesions and almost seven times as often severe periventricular white matter lesions than in subjects with the APOE3E3 genotype. We consider it unlikely that the APOE*4 allele alone is responsible for this association, because then we would expect to find an even higher association for the APOE4E4 carriers with white matter lesions. On the other hand, Slooter et al showed a protective effect of the APOE*2 allele for atherosclerosis and dementia, [21,24] both of which have been positively related to white matter lesions. This makes it unlikely that the APOE*2 allele is responsible for the increased risk for white matter lesions in individuals with the APOE2E4 genotype. Perhaps it is a chance finding.

Our finding of a 1.5 times increase in risk for white matter lesions in carriers of the APOE*4 allele is in line with previous studies.[7,8] That the

observed association was not statistically significant may be the result of the relatively small sample size. In a larger study, including over 3000 persons, a significant relation was found, with the same risk estimate. 7 It is not known how the APOE*4 allele influences the presence of white matter lesions. A possible explanation may be an impairment of neuronal repair.[15,16,25] Neuronal repair is an important process in restoring the integrity of the brain in response to injury, for example after a period of ischemia. Animal studies have shown that chronic hypo-perfusion of the white matter can result in white matter lesions.[26] Individuals with an APOE*4 allele may be at increased risk for white matter lesions because of this impaired response to cerebral injury, and this in turn may underlie the observed association between APOE*4 and the risk for dementia [10,24]

In conclusion, we found among carriers of the APOE*4 allele a significantly increased volume of the subcortical white matter lesions, especially in those with an APOE2E4 genotype. Subjects with the APOE2E4 genotype also had the highest degree of periventricular white matter lesions. It may be that this association explains, at least in part, the increased risk for carriers of the APOE*4 gene for cognitive decline and dementia that was found by others. Prospective follow up studies, with the use of neuro-imaging, are needed to clarify the possible interaction between APOE, white matter lesions and consequent cognitive decline and dementia.

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Chapter 6

General discussion

This thesis describes frequency and risk factors of cerebral white matter lesions in the general population. It is based on data from the Rotterdam Scan Study, a prospective population based study on determinants and consequences of age related brain changes among 1084 subjects aged between 60-90 years.

In this chapter, the main findings will be summarized with reference to the results from other studies. In addition general methodological aspects of the study will be discussed. Inference of the results from our studies will be made and there is a discussion on the possible clinical implications of the presence of white matter lesions. Finally, recommendations for future research will be made.

Background

White matter lesions are frequently found on cerebral magnetic resonance imaging scans of elderly non-demented and demented people.[1-4] They are considered to mainly reflect small vessel pathology, however their pathogenesis remains unclear. Age, increasing diastolic and systolic blood pressure levels and indicators of atherosclerosis have consistently been reported as risk factors for white matter lesions, regardless of their location.[2-5] There are many other, particularly vascular, risk factors that have been associated with white matter lesions; but the nature of these relations is unclear and they are not consistent throughout studies.

There is growing evidence that white matter lesions play an important role in the development of cognitive decline and dementia.[4,6-8] The white matter can be distinguished into two separate anatomical regions, namely the periventricular white matter (a strip of white matter adjacent to the lateral ventricles) and the subcortical white matter (the white matter just underneath the gray matter). However, only a few studies distinguish these two locations and report on risk factors for lesions in these regions separately, whereas different risk factors may underlie white matter lesions at different locations.[9,10] There is evidence that especially periventricular white matter lesions are related to cognitive decline,[11,12] whereas subcortical white matter lesions may be related with late-onset depression.[12,13] It is therefore important to distinguish between these two locations.

To date, the associations found are mainly from cross-sectional MRI studies among elderly people. However, the well-established risk factors hypertension and atherosclerosis already occur early in life, when the prevalence of white matter lesions is still low. In order to gain more insight in the causation of white matter lesions a study with a long-follow-

up would be very informative. In addition to this, many risk factors are more discriminative at lower age (when the prevalence of the risk factor is still low) than at higher ages.

The studies presented in this thesis describe the association between vascular risk factors and white matter lesions in a longitudinal population-based study among 1084 subjects, aged 60-90 years. The study was carried out in 1995-1996.

Main Findings

Frequency distribution of white matter lesions

Of all participants 20% and 8% were completely free of periventricular or subcortical white matter lesions, respectively. This means that a vast majority of the elderly has white matter lesions to some extent. This is in agreement with findings from others who reported a prevalence ranging from 5 to 90 percent, depending on study design, study population and white matter lesions rating scales.[2-4,14-17] It may be more informative to describe the frequency distribution (range) of white matter lesions, because if almost every subject has white matter lesions one cannot identify a risk factor for those lesions, whereas one may find risk factors that influence the frequency distribution, i.e. which factors cause a shift upward or downward of the frequency distribution (for example age in figure 1, chapter 2.2.). Our study confirmed findings by others of an increased prevalence and severity of white matter lesions among women.[2-4] We showed that this was mainly due to a significantly higher degree of subcortical and periventricular white matter lesions in the frontal region.

Risk Factors

Blood pressure and hypertension

Baseline and cross-sectional diastolic and systolic blood pressure level was significantly associated with the presence of both types of white matter lesions. We found about a 20% to 30% increased risk for the presence of white matter lesions per 10 mm Hg increase in both baseline and cross-sectional blood pressure level. Recent results from the NHLBI-study also reported a significant association between blood pressure levels measured about 30 years ago and white matter lesions.[18] To our knowledge there are no other studies with a follow up of this duration. The cross-sectional findings are in line with the associations others found.[2-4]

In addition we studied the presence of white matter lesions as a function of blood pressure change over time. We found about a doubled risk for both types of white matter lesions in subjects with a decrease or increase in diastolic blood pressure of 10 mm Hg or more, over a 20 years period. There was no such relation for systolic blood pressure. This J-shaped association between diastolic blood pressure and both types of white matter lesions was especially marked in subjects with a history of myocardial infarction, whereas this relation was linear in subjects without a history of myocardial infarction. There was a linear relation between systolic blood pressure and white matter lesions, regardless of a history of myocardial infarction. To date, others have not described this relation. In accordance with our observations, other studies among elderly subjects suggested that both a low and high diastolic blood pressure are associated with increased risk of cardiovascular disease, in particular among subjects with preexisting heart disease.[19-22]

The relation between increasing level of blood pressure and white matter lesions was further extended to the relation with hypertension. When a risk factor is related to mortality, selective survival may affect the relation between this risk factor and an outcome. Indeed, we found that the risk estimates in the study population as a whole were biased and we showed that the most unbiased risk estimates are in the 60-70 years age category. In the cross-sectional analysis of the whole study population, we found an about two-fold increased risk for both types of lesions for subjects with hypertension. This was very much in agreement with findings by Breteler et al and Liao et al, who also reported an approximately two times higher risk for white matter lesions for subjects with hypertension.[2, 3] For subjects aged between 60-70 years we found that subjects with hypertension had an almost five-fold increased risk for subcortical white matter lesions and an almost three-fold increased risk for subcortical and periventricular white matter lesions. When duration of hypertension was considered we found a sixteen- to twenty-fold increase in risk for periventricular and subcortical white matter lesions respectively, if individuals had hypertension for more than 20 years. There are currently no studies that have addressed this topic.

Indicators of atherosclerosis

We investigated the association between mid-life or late-life aortic atherosclerosis and white matter lesions. Individuals who had already signs of aortic atherosclerosis on an abdominal X-ray during mid-life, had a two and a half fold increased risk for periventricular white matter lesions, whereas there was no relation with subcortical lesions. We also found

that the degree of mid-life aortic atherosclerosis predicts the severity of periventricular white matter lesions later in life in a dose dependent fashion. There was no relation between late-life aortic atherosclerosis and white matter lesions.

In addition we investigated the association between indicators of carotid atherosclerosis (intima media thickness and the plaques) and white matter lesions, in a cross-sectional design. There was a relation between carotid atherosclerosis and periventricular white matter lesions, whereas this relation was less clear for subcortical white matter lesions. The relation between indicators of atherosclerosis and white matter lesions has also been examined by others,[4,5] who reported similar associations.

We found a clear relation between current atrial fibrillation and the presence of periventricular white matter lesions, but not for subcortical white matter lesions. Subjects with atrial fibrillation had more than twice as often severe periventricular white matter lesions but not subcortical white matter lesions. Similar associations have been described by Ylikoski et al and Lindgren et al.[9,10] In contrast to our findings, Ylikoski et al found this relation especially for subcortical white matter lesions and not for those in the periventricular region. This may be because of a difference in the white matter lesions rating scale between the studies. The maximum degree of periventricular white matter lesions was a nodular band in their rating scale, whereas subcortical white matter lesions extending deep in the white matter to the ventricles, were considered to be in the subcortical region. For this reason it may be that the most severe white matter lesions were allocated to different regions in the two studies; i.e. to the periventricular region in our study and to the subcortical region in the study of Ylikoski et al.[9]

A high-risk subgroup with atrial fibrillation and left ventricular hypertrophy had a seven-fold increased risk for periventricular white matter lesions, whereas for subcortical white matter lesions no such association was observed.

Vasomotor reactivity reflects the ability of small cerebral arteries to dilate under the influence of certain stimuli, like carbon dioxide, in order to increase cerebral blood flow in case of increased demands. Atherosclerosis may disturb the integrity and function of the arterial wall and thereby its capacity to dilate in reaction to these stimuli. We found a 30% to 50% reduced risk per 10% increase in vasomotor reactivity for the presence of periventricular and subcortical white matter lesions, respectively. This finding was in agreement with others who reported impaired cerebral haemodynamics in subjects with white matter lesions.[23-26] Another explanation may be that an impaired vasomotor reactivity is the

functional representation of the structural changes in the brain that white matter lesions are.

Apolipoprotein E genotype

Finally we examined the relation between the apolipoprotein E genotype and white matter lesions. To date, there is only a single study that addressed the possible role of the apolipoprotein E genotype (APOE) in white matter lesions.[27] In addition, Schmidt et al investigated the association between the APOE genotype on the one hand and microangiopathy related cerebral damage on the other.[28] It is well established that the APOE*4 allele of the gene is associated with an increased risk of cognitive decline and dementia, possibly in particular in the presence of atherosclerosis.[29] How the APOE*4 allele increases the risk for cognitive decline and dementia is not known, though it is suggested that cerebral white matter lesions are involved. [30]

When we did the analysis on all individuals with an APOE*4 allele (those with the APOE3E3 genotype forming the reference group) APOE*4 carriers had a borderline significantly increased risk of 50% for both types of lesions. We found an about seven-fold and two-fold increased risks for carriers of the APOE2E4 allele for periventricular lesions and subcortical white matter lesions compared to APOE3E3 carriers respectively, whereas Schmidt et al found that carriers of the APOE2E3 allele had more often microangiopathy related cerebral damage than APOE3E3 carriers.[28] We have no explanation for this discrepancy. Our finding of a one and a half time increased risk for white matter lesions in carriers of the APOE*4 allele is in line with previous studies.[27,28] That the observed association was not statistically significant may be the result of the relatively small sample size. This is supported by the results from a larger study, including over 3000 persons, in which a significant relation, with the same risk estimate, was found.[27]

Methodological considerations

There are two major issues that should be considered when a study is judged on its methodological merits, namely validity and precision. Validity deals with the generalizability (external validity) and the amount of bias (internal validity). There are three types of biases to be distinguished, namely selection bias, information bias and confounding. They will be discussed in the following sections. Precision deals with the amount of

random error in a study and is basically about the reproducibility of a study, and will be discussed after the section on validity.

Selection bias

A major threat to the validity of a study is selective non-response. Selection bias in a follow up study occurs if participation is related to the outcome under study, in this case white matter lesions.

However, direct quantification of the effect of selective non-response is difficult since the degree of white matter lesions is not known among non-responders. A general assumption is that associations between risk factors and an outcome are different in non-responders than in responders. An indirect way for assessing the effect of selective non-response is by comparing baseline risk factors for white matter lesions between responders and non-responders. In our study the overall response rate was 63%, and declined from 73% among subjects aged between 60-70 years to 48% among participants aged between 80-90 years in 1995-1996. The lower the response rate, the higher the potential for selection bias. Yet we found only small, mainly non-significant, differences with respect to baseline risk factors between responders and non-responders and this difference did not vary across the age-strata.

Another source of selection bias is survival bias. Since we conducted a prospective study with a long follow-up period, a certain proportion of the baseline cohort will have died. How could this selective mortality affect the associations we found? Since cardiovascular disease is a major cause of death among the elderly we consider it likely that especially individuals with one or more cardiovascular risk factors would have died. This is in line with our observation of a lower baseline prevalence of hypertension in survivors than in those who had died before the follow up. This difference increased with age. Furthermore, even if individuals with cardiovascular risk factors had not died, one might assume that these risk factors were less severe or did not have such a deleterious effect on their cardiovascular and probably cerebrovascular system. Therefore one would expect that the association between a vascular risk factor and white matter lesions would be weak in the highest age category. This is supported by our findings. It is therefore likely that the most unbiased risk estimates are found in the lowest age category. In this age category we generally found the highest relative risks, especially in the Zoetermeer sub-population.

Confounding

Any association between a risk factor and an outcome variable may be attributable to another variable, which may not have been taken into ac-

count, a so-called confounder. A confounder is associated with both the determinant and the outcome under study and is not an intermediate factor in the causal chain leading to the outcome variable under study. A way to deal with confounding in epidemiological studies is to control for it in the analysis. For example age was an important confounder in our study, because it had significant relations both with any risk factor we studied and with either type of white matter lesions.

Since the risk factors we studied are closely related to atherosclerosis, the observed associations may be confounded by cardiovascular risk factors such as diabetes, body mass index and hypertension. Adjustments were made to control for possible confounding by these factors. Throughout our studies adjustments for cardiovascular risk factors did not significantly alter the observed associations between a risk factor and white matter lesions. This suggests that the associations described between the risk factors for white matter lesions described in this thesis cannot, or can only partly be attributed to confounding by other cardiovascular risk factors. This may possibly indicate that white matter lesions are independently related to, and perhaps a consequence of, the risk factors described.

Information bias – Misclassification of white matter lesions

Misclassification can occur in the determinant, the confounder and the outcome and can be related or not be related to the outcome or determinant (differential or non-differential).

White matter lesions were rated by means of a specially designed rating scale and were distinguished into those in the periventricular and in the subcortical region. Our rating scale was much more sensitive than that used by many others, because each lesion, however small, was counted separately. Through double reading and extensive inter- and intra-rater studies we attempted to minimize misclassification of the lesions. We cannot exclude the possibility that we could not always make the proper distinction with respect to periventricular or subcortical location of the lesions, especially if white matter lesions were extensive. However, all readers were blinded to the results of the risk factors and the cognitive status. Any misclassification would therefore be non-differential and would have biased our findings towards the null hypothesis.

Information bias – Misclassification of the determinant

An important methodological issue in this thesis is the validity of the measurements of the determinants. Differential error may occur when determinants are assessed differently among those with white matter le-

sions and in those without. It is unlikely that this has happened in our study because data on determinants were already obtained before the assessment of a MRI scan, and data collection can therefore by no means be related to the outcome. However, since perfect assessment of the determinants is hypothetical, non-differential error is unavoidable to some extent. The major point of concern of random misclassification is dilution of the association towards the null hypothesis. An important point in our studies is the validity of the various atherosclerosis measurements. As for the validity of radiographic assessment of aortic calcification for the diagnosis of atherosclerosis, it was shown in an autopsy study that radiographically detected aortic calcification represented true intimal atherosclerosis.[31] On comparison with computed tomography it appeared that calcifications seen on the X-ray were located in the vessel wall in all cases.[32]

Increased carotid intima-media thickness not necessarily reflects atherosclerosis. It may merely reflect an adaptation of the vessel wall in a response to changes in shear stress and tensile stress.[33] However, in several studies ultrasonographically detected increased carotid wall thickness and its progression was found to be associated with cardiovascular risk factors.[34-36] These findings are in favor of the idea that increased carotid wall thickness, as detected by ultrasonography, reflects a valid measurement of atherosclerosis.

All atherosclerosis indicators were based on single measurements. This may have led to misclassification. However, we consider it unlikely that such misclassification is related to the extent of white matter lesions; therefore it would have biased our findings towards the null hypothesis.

Misclassification may also have occurred in the relation between atrial fibrillation and white matter lesions. We probably underdiagnosed the prevalence of atrial fibrillation since we only used a single 10-second resting ECG for the detection of rhythm disturbances. We therefore could not detect all episodes of paroxysmal atrial fibrillation. Findings by Manolio et al indicate that 74% of all patients with atrial fibrillation identified during a 24-hour ambulatory ECG assessment are detected with a 10 second ECG recording.[37] Since this misclassification is not related to presence of white matter lesions and is therefore non-differential, it will only have reduced the strength of the association between atrial fibrillation and white matter lesions towards the null hypothesis.

Precision

Precision reflects the amount of random error in a given measurement and thereby affects reproducibility of that measurement. One way to increase overall precision is to increase the precision of any single meas-

urement; the other is by increasing the number of measurements. In Rotterdam Scan Study we dealt with this problem by measuring both the outcome and any determinant by means of validated procedures and by performing duplo measurements.

Pathogenesis of white matter lesions

Nowadays there are a few hypotheses about the development of age related white matter lesions, which are not mutually exclusive. One hypothesis suggests an ischemic origin of white matter lesions. This explanation is based on the associations found in epidemiological studies between vascular risk factors and white matter lesions.[2-4] It is also supported by experimental studies of cerebral ischemia in animals.[38,39] The other hypothesis suggests that white matter lesions are secondary to expansion of the cerebral ventricles and is based on the frequent finding of especially periventricular white matter lesions in subjects with so called normal pressure hydrocephalus.[39,40]

The first hypothesis is that white matter lesions are a consequence of cerebral ischemia, possibly caused by cerebral hypoperfusion. Current opinion is that (long-lasting) hypertension induces vessel wall alterations (arteriolosclerosis) leading to narrowing of the vessel lumen, ultimately, resulting in white matter ischemia.[39,41,42] Thanks to the long follow-up in part of our study we had the unique opportunity to further explore this hypothesis and to identify some intermediate factors in the development of white matter lesions.

If hypertension had been present for a period of more than 20 years, the relative risk for white matter lesions increased about 20-fold in the most unbiased age-stratum of the study population, compared to normotensive subjects. The pathophysiological process by which hypertension leads to disease is the induction of atherosclerosis and hypertrophy in the wall of large or small arteries.[41,42] It is therefore plausible to argue that atherosclerosis may underlie the association between hypertension and white matter lesions. Indeed, we observed a dose-dependent relation between severity of aortic atherosclerosis, as measured 20 years ago, and white matter lesions in the Zoetermeer sub-population. We could not establish whether hypertension was the result of atherosclerosis or that this relation was the other way around, because the change of aortic atherosclerosis over time was not measured. However there are some clues from our study that support a primary role for atherosclerosis in the pathogenesis of white matter lesions. The first of these is our finding of a J-shaped relation between a change in diastolic blood pressure over a 20-

year period and white matter lesions. This favors the involvement of atherosclerosis in the pathogenesis of white matter lesions, because a J-shaped association has also been reported for the progression of atherosclerosis as a function of change in diastolic blood pressure.[32] Secondly, we showed an association between indicators of atherosclerosis and white matter lesions in the cross-sectional analyses.

Another hypothesis was proposed because of a high prevalence of white matter lesions,[43] especially in the periventricular region, in subjects with normal pressure hydrocephalus. There are basically two explanations for this finding. One is that, despite the name of the disorder, periods of increased cerebrospinal fluid pressure occur in subjects with dilated ventricles through some disorder of cerebrospinal fluid circulation,[40,44] and that this raises the pressure in the surrounding periventricular white matter.[45] The resulting ischemia leads to the pathological hallmarks of white matter lesions and the typical MRI picture of periventricular white matter lesions. The other explanation is increased leakage of cerebrospinal fluid due to an impaired barrier function of the ependymal lining of the ventricles. This results in leakage of cerebrospinal fluid into the surrounding tissue (i.e. the periventricular white matter). In this view, a second factor consists of alterations in the vessel wall caused by the earlier mentioned risk factors for white matter lesions (hypertension, atherosclerosis), that hinder reabsorption of this cerebrospinal fluid from the parenchyma.[46,47] However the issue is whether normal pressure hydrocephalus being a true cause or rather the consequence of white matter lesions. White matter lesions in the periventricular region may not only occur as a result of normal pressure hydrocephalus, but widening of the ventricles may also occur ex-vacuo as a result of white matter lesions. Until now it is not clear whether normal pressure hydrocephalus and especially periventricular white matter lesions should be considered as two different entities or that they linked in a single causal chain, in which it is debated which is the cause or which is the consequence. To my knowledge there is no evidence for a relation between normal pressure hydrocephalus and subcortical white matter lesions and our study has no data on this either.

How can these findings be combined into a plausible explanation for the development of white matter lesions? A possible explanation might be that among persons with advanced atherosclerosis and hypertrophy of the vascular tree, often on the basis of longstanding hypertension, cerebral autoregulation is impaired.[48] In healthy individuals the cerebral blood flow is maintained via the mechanism of autoregulation, which compensates for a reduction or increase of blood pressure, across a certain range.[48] As a result of the impaired autoregulation, the lower limit of

blood pressure at which the autoregulation still functions properly shifts towards a higher blood pressure level,[48,49] so that even normal levels of blood pressure may result in hypoperfusion of the white matter in these persons.[50] This reduction of cerebral blood flow will primarily affect areas with an already marginal blood supply under physiological conditions, such as the subcortical and periventricular white matter.[39,51,52] Indeed, an impaired autoregulation and a reduction of cerebral blood flow has been demonstrated in subjects with periventricular white matter lesions.[25,26] Although the cross-sectional design of the studies did not allow a conclusion about the white matter lesions being a cause or a consequence of a reduction of cerebral blood flow.

Another adaptive response to prevent the brain from hypoperfusion is the so-called vasomotor reactivity, which is based on the ability of the small arteries in the brain to dilate under the influence of chemical stimuli (mainly carbon dioxide), thereby increasing cerebral blood flow.[53] It is known that this response can be affected by atherosclerotic changes of the vessel wall.[54] It can be hypothesized that an impaired vasomotor response can no longer compensate for a reduction of cerebral blood flow, presumably by the inability of the atherosclerotic arteriole to dilate any further. This may result in ischemia. The notion that (chronic) cerebral hypoperfusion may indeed play a role in the development of white matter lesions was confirmed by our finding of an inverse association between vasomotor reactivity and the presence of white matter lesions.

Another indication that cerebral hypoperfusion may be involved in the pathogenesis of white matter lesions comes from our finding of a J-shaped association between diastolic blood pressure and white matter lesions in subjects with a history of a myocardial infarction (representing advanced vascular disease), and not in those without. In contrast, in people who have had a low diastolic blood pressure all their life the autoregulation is not impaired, and therefore they have a normal cerebral blood flow, even at a low blood pressure level. In our study those subjects indeed showed the lowest rate of white matter lesions.

Further evidence for a role of cerebral hypoperfusion in the development of white matter lesions comes from the association between atrial fibrillation and white matter lesions. Subjects with this disorder have a reduced cardiac output.[55] Especially among the elderly, who may already have a compromised cerebral circulation, this can lead to a reduction in cerebral blood flow.[55-57] Given that a reduced cerebral perfusion precipitates the development of white matter lesions we would expect an even higher risk for subjects with atrial fibrillation and left ventricular hypertrophy, in whom the circulation is even more compromised.[55,58] Indeed we found an about seven fold increase in risk for those individuals. We considered the

possibility of white matter lesions being secondary to the formation of thrombi less likely, because in that case we would expect a stronger association between atrial fibrillation and white matter lesions among subjects with evidence of cerebral infarction on MRI scanning.

Most associations we found were strongest for the periventricular white matter lesions, whereas this was less clear for the subcortical region. This suggests that different factors may underlie periventricular and subcortical white matter lesions, or at least that the periventricular region is more susceptible for a reduction in cerebral blood flow. The periventricular white matter is an arterial border zone that is already marginally perfused under physiological circumstances, which makes it especially vulnerable by a decrease of cerebral blood flow.[25,39,52] In contrast, the subcortical white matter is not an arterial watershed area,[59] though at high ages, the long penetrating arteries supplying the subcortical white matter undergo atherosclerotic changes, that may lead to a reduction in blood flow in that area.[50]

On the basis of our findings the following chain of events may be proposed for the development of white matter lesions. Long-lasting hypertension gradually induces hypertrophic and degenerative changes in the vessel wall of the arterioles of the white matter. This results in impairment of haemodynamic responses, i.e. cerebral autoregulation and vasomotor reactivity. During episodes of an increased demand for cerebral blood flow, no compensatory mechanisms are left anymore. This may lead to hypoperfusion and eventually to ischemia. If the periods of ischemia last too long, or occur too frequently, the myelin and axons degenerate, leading to the typical MRI picture of white matter lesions.

Clinical implications

A clinically relevant finding was our observation of a lower risk for both types of lesions in subjects with an adequately treated hypertension (i.e. a systolic blood pressure below 160 mm Hg and a diastolic blood pressure below 95 mm Hg) than in individuals with uncontrolled hypertension. We suggested that our findings are consistent with the view that adequate treatment reduces the presence of both types of white matter lesions and may thereby also prevent or reduce the attendant cognitive impairment or dementia.

These observations should be interpreted with caution and may not apply to all elderly subjects. For persons with overt cardiovascular disease it may be that the optimum achievable blood pressure is not necessarily synonymous with the lowest diastolic blood pressure.[19-22,60,61] This was

supported by our finding of a J-shaped association between a substantial decrease or increase in diastolic blood pressure and the risk for white matter lesions. This J-curve could be largely attributed to the subjects with a myocardial infarction. These findings are consistent with studies that reported a J-shaped association between diastolic blood pressure and the risk of cardiovascular disease among subjects with preexisting heart disease.[19-22] The clinical relevance of these findings may be that hypertension should as a rule be treated in an elderly population, but lowering of the diastolic blood pressure to 'normal' values should be avoided in the high-risk group of elderly subjects with prevalent cardiovascular disease.

Considering the high prevalence of both types of white matter lesions in the elderly and the serious clinical implications, it would be useful to identify individuals at risk for white matter lesions relatively early in life.[12] We tried to investigate this by relating baseline data on atherosclerosis from the Zoetermeer Study (1975-1978) to the presence of cerebral white matter lesions later in life. We found that presence of aortic atherosclerosis during mid-life predicts white matter lesions in later life. This may indicate that there is a long interval between the presence of aortic atherosclerosis and the emergence of white matter lesions. Any preventive intervention should therefore preferably take place in the early stages of atherosclerosis.

Treatment

The relation between hypertension or other vascular factors and white matter lesions is well established,[2-4] as is the association between cognitive impairment and white matter lesions. In addition, our study provides evidence for a relation between atrial fibrillation and white matter lesions. There are clues that hypertension and atrial fibrillation are related to cognitive impairment and dementia.[7,62-65] Our study and findings of the Cardiovascular Health Study are consistent with the view that effective treatment of hypertension may reduce the risk for white matter lesions.[3] We could not investigate the effect of treatment of atrial fibrillation on the presence of white matter lesions in our study.

Despite these observations, experimental research is the only method to establish a firm causal relationship between a certain determinant and its outcome. For some risk factors described in this thesis experimental research would be premature, but hypertension and atrial fibrillation may be good candidates for experimental research on their role in the development of white matter lesions. Theoretically, a double blind randomized

trial on the effects of treatment of these particular risk factors would be the best design to study the causal links between hypertension or atrial fibrillation and the occurrence of white matter lesions. This design minimizes the occurrence of bias (unknown confounders, confounding by indication, blind assessment of outcome). However, such a trial would only be clinically acceptable and relevant if not merely the degree of white matter lesions was the measure of outcome, but rather cognitive performance. If any treatment would only reduce the risk of white matter lesions without improving cognitive function, or prevent further impairment, treatment would not be a wise thing to undertake. The notion of treatment is supported by recent findings of the Syst-Eur investigators who found that treatment of isolated systolic hypertension reduced the incidence of dementia.[66] Although they did not provide any data on white matter lesions or other brain features, their findings make a randomized trial on the effect of anti-hypertensive treatment on white matter lesions superfluous and unethical, even apart from the beneficial effect on other organ system. An option to improve our knowledge on the understanding of the development of white matter lesions may be the inclusion of neuroimaging in new trials that study the effects of antihypertensive medication on vascular events in general.

The same argument applies to atrial fibrillation. There are many studies on atrial fibrillation, its treatment and stroke.[67] In those studies inclusion of a neuropsychological test battery and neuroimaging may provide more information about the nature of the relation between atrial fibrillation and cognitive impairment and dementia.

Future research

White matter lesions in the brain are a major challenge for medicine, since the prevalence of these lesions is very high among the elderly, and even severe white matter lesions are present in a considerable proportion of 'healthy' elderly subjects. It is getting more and more clear that these lesions are important in the development of cognitive decline and depression with a late-life onset.[12] Dementia represents the end stage of cognitive impairment, occurring in relatively few people, whereas lesser degrees of intellectual handicaps are much more common. Yet these 'minor' cognitive defects may seriously affect the quality of life.

Since it is suggested that especially the more severe white matter lesions are related to cognitive impairment[11, 12] or depression[12, 13] it is of great importance to study risk factors that are associated with an increase of severity of preexisting white matter lesions. Future prospective

studies should address these questions. Due to the cross-sectional design in the studies on white matter lesions thus far, risk factors of changes in the severity of white matter lesions have not been identified yet.

As discussed before our study indicated the potential role of cerebral hypoperfusion in the pathogenesis of white matter lesions. Since in our study a relatively indirect indicator of cerebral perfusion, the vasomotor reactivity, was measured in only a small subset of 80 persons, the objective of a future study may be to assess the role of cerebral blood flow in the development of white matter lesions. In my opinion those measurements should be carried out in a prospective way, whereas cross-sectional analyses seem of less value, because a reduction of cerebral blood flow in areas of white matter lesions are not surprising. Possible techniques would be the measurement of (regional) cerebral blood flow by means of perfusion measured with MRI techniques, single photon emission computed tomography (SPECT), or positron emission tomography (PET). Our results suggested a sex difference in the frequency distribution of those lesions, and we suggested that a reduction of cerebral blood flow, possible by means of a reduction of estrogen levels in post-menopausal women, might underlie this association. This warrants further investigation.

Our study has provided further knowledge on the risk factors for white matter lesions. Some risk factors we addressed can be modified, as suggested by our finding that effective treatment of hypertension can reduce the risk of white matter lesions. As discussed before it is particularly important to design a randomized clinical trial to properly investigate these questions.

A common observation in our studies was that the associations were strongest in the age category from 60-70 years, especially if the risk factor under study was assessed 20 years ago (The Zoetermeer sub-population). This is probably explained by selective mortality and a reduced discriminative power of a risk factor at higher ages, as discussed before in this chapter. Future studies therefore should try to include people early in mid-life (30-40 years), or if that is not possible, collect data on risk factors on that period. This might be an effective strategy to detect people at risk for white matter lesions (and possibly for cognitive decline) relatively early in life, thus opening the way for prevention or reduction of severity. A major drawback of this option is that it will take a long time before the outcome under study occurs.

In addition, future studies should be large enough to identify specific sub-groups that may be at an increased risk for white matter lesions. Our study showed that subjects who had a decrease or increase of over 10 mm Hg in diastolic blood pressure had an increased risk for white matter lesions. It has been suggested that prevalent cardiovascular disease, or hy-

pertension and its treatment play an important role in this J-curve. However, because of the small numbers in these particular subgroups we were not able to further address this topic. The same was true for subjects with atrial fibrillation and left ventricular hypertrophy. They appeared to have a greatly increased risk for white matter lesions, but the small numbers (n=7 among 1084 participants) did not allow further exploration of this association.

Since the determinants for white matter lesions as hypertension and atherosclerosis interact in an intricate temporal framework a follow-up study is essential to disentangle the causal role of the risk factors we studied or to establish that they in turn are consequences of preceding factors.

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Summary

This thesis describes the frequency distribution and the risk factors of cerebral white matter lesions. There is increasing evidence that these lesions play a role in the development of cognitive decline and dementia. These mental illnesses have an enormous impact on health care systems as a whole and for the individual affected, including his or her relatives, especially in our aging societies. However, these lesions also frequently occur in healthy, non demented subjects, but to what extent is yet not clear. Early detection of persons at risk for these illnesses offers potential for early intervention and possible treatment of these disorders. Therefore the aim of this thesis was to investigate the frequency distribution and risk factors for white matter lesions in a healthy population of non-demented elderly. The study was performed in the Rotterdam Scan Study.

The Rotterdam Scan Study was designed to study determinants and consequences of age related brain abnormalities in the elderly. In 1995-1996, 1904 subjects aged between 60-90 years were randomly selected in strata of age (5 years) and sex from two large ongoing prospective follow-up cohort studies, the Zoetermeer Study and the Rotterdam Study. From 1724 eligible subjects 1084 participated (response rate 63%). The Zoetermeer Study is a prospective population-based study among 10361 subjects, aged between 5-91 years at baseline, which originally addressed determinants of chronic diseases. It had its baseline data-collection from 1975-1978; the mean follow up period was 19.6 years. Due to its long-follow up data from this study enables us to investigate the relation between a certain risk factor present already relatively early in life and the presence of white matter lesions later in life. The Rotterdam Study had the baseline data collection from 1990-1993; mean follow up period was 4.8 years. The Rotterdam Study is a population-based prospective cohort study, among 7983 elderly subjects aged 55 years and over, investigating determinants of neurological, cardiovascular, locomotor and ophthalmologic diseases in the elderly. This led us to investigate the relation between risk factors late in life and the presence of white matter lesions only a few years later.

For the Rotterdam Scan Study a white matter lesions rating scale was designed which distinguished lesions in the subcortical and periventricular region. Lesions were rated per size and location in those two regions.

Chapter 2.1. presents a review on the frequency and risk factors of cerebral white matter lesions, based on literature data, while **chapter 2.2.** presents the age and sex specific frequency distribution of white matter lesions in the Rotterdam Scan Study. We found a significant association between age and presence of white matter lesions. Women had significantly more (severe) white matter lesions, especially in the frontal region.

Chapter 3 deals with the relation between blood pressure and white matter lesions. It is suggested that a change of diastolic blood pressure may be a better predictor of cardiovascular disease than the actual level of blood pressure, since the latter is the resultant of life-long exposure to factors that have influenced the blood pressure, but does not provide information on the previous blood pressure level. In accordance with that observation, other studies among elderly subjects suggested that both a low and high diastolic blood pressure are associated with increased risk of cardiovascular disease, in particular among subjects with preexisting heart disease. Therefore in **chapter 3.1.** the association between a decrease or an increase of blood pressure over a 20 years period and white matter lesions is described. We found about a doubled risk for both types of white matter lesions in subjects with a decrease or increase in diastolic blood pressure of 10 mm Hg or more, over a 20 years period. There was no such relation for systolic blood pressure. This J-shaped association was also present between diastolic blood pressure and both types of white matter lesions in subjects with a history of myocardial infarction, whereas this relation was linear in subjects without a history of myocardial infarction. There was a linear relation between systolic blood pressure and white matter lesions in subjects with or without a history of myocardial infarction. **Chapter 3.2.** describes the relation between duration of hypertension and its treatment and white matter lesions. When studying a risk factor that is related to mortality selective survival may affect the relation between a risk factor and an outcome. We showed that the most unbiased risk estimates are in the 60-70 years age category. In this age group we found a 16- to 20-fold increased risk for periventricular and subcortical white matter lesions respectively, for individuals who had hypertension for more than 20 years. In addition we showed that effective treatment of hypertension reduced the risk for white matter lesions.

Chapter 4 describes the relation between atherosclerosis and atherosclerosis related disorders. In **chapter 4.1.** we present the association between mid-life and late-life aortic atherosclerosis and white matter lesions. Individuals who had already signs of aortic atherosclerosis during mid-life had a two and a half fold increased risk for periventricular white matter lesions, whereas there was no relation with subcortical lesions. We found that mid-life aortic atherosclerosis predicts periventricular white matter lesions later in life in a dose dependent fashion. There was no relation between late-life aortic atherosclerosis and white matter lesions. In chapter **4.2.** we report an association between indicators of carotid atherosclerosis and periventricular white matter lesions, whereas this relation was less clear for subcortical white matter lesions. People with peripheral arterial disease had only a slight increased volume of subcortical

white matter lesions compared to those without, whereas for periventricular white matter lesions there was no difference (**chapter 4.2.**). **Chapter 4.3.** reports on the association between atrial fibrillation and white matter lesions. Subjects with atrial fibrillation had more than twice as often severe periventricular white matter lesions but not subcortical white matter lesions. A high risk subgroup with atrial fibrillation combined with left ventricular hypertrophy had a seven-fold increased risk for periventricular white matter lesions and not for subcortical white matter lesions. Our results suggested that cerebral hypoperfusion was the most likely mechanism for the presence of white matter lesions, instead of atrial fibrillation induced emboli. This association might underlie the association between atrial fibrillation and dementia.

Vasomotor reactivity reflects the ability of small cerebral arteries to dilate under the influence of certain stimuli, like carbon dioxide, in order to increase cerebral blood flow in case of increased demands. Atherosclerosis may disturb the integrity and function of the arterial wall and thereby its capacity to dilate on these stimuli. For that reason we investigated the role of vasomotor reactivity in white matter lesions (**Chapter 4.4.**). We found a 30-50% reduced risk per 10% increase in vasomotor reactivity for the presence of periventricular and subcortical white matter lesions, respectively.

Finally, we examined the relation between the Apolipoprotein E genotype and white matter lesions (**Chapter 5**). Only a few studies investigated the relation between white matter lesions and the apolipoprotein E genotype. Previous studies found an association between the APOE*4 genotype and dementia. It has been suggested that white matter lesions might underlie this relation. We found an about seven-fold or a two-fold increased risk for carriers of the APOE2E4 allele for periventricular lesions and subcortical white matter lesions compared to APOE3E3 carriers respectively. When we did the analysis on all individuals with an APOE*4 allele compared to those with the APOE3E3 genotype APOE*4 carriers had a borderline significantly increased risk of 50% for both types of lesions.

In **Chapter 6** the results of our study are discussed. We conclude that the prevalence of white matter lesions is high in the elderly, but that especially severe white matter lesions appear to be of importance for cognitive consequences. We found an association between classical cardiovascular risk factors and white matter lesions. Our results indicate the importance of detection of the risk factors already early in life because those are the people at the highest risk for white matter lesions, with probably the best chances for therapeutic intervention. On the basis of our results we hypothesized that white matter lesions are caused by long-lasting presence of cardiovascular risk factors, leading to atherosclerosis.

Atherosclerosis of the small arteries in the white matter may be responsible for an inadequate reaction on increased demands for blood supply, leading to hypoperfusion of the white matter. There is now convincing evidence of a relation between white matter lesions and cognitive impairment. Possible treatable vascular risk factors have been identified as important risk factors for these lesions. Results from our study suggest that treatment of hypertension reduces the risk for white matter lesions. Another risk factor for which potentially adequate treatment is available is atrial fibrillation. This would make hypertension and atrial fibrillation a good candidate for a randomized clinical trial on the effects of treatment of these risk factors on white matter lesions and cognition. Because of ethical reasons and for reasons of efficacy such a trial should preferably be executed within the framework of an ongoing trial on for example treatment of hypertension, or atrial fibrillation, and the incidence of cardiovascular disease.

Samenvatting

Dit proefschrift richt zich op de factoren die ten grondslag liggen aan witte stofafwijkingen in de hersenen. Dergelijke witte stofafwijkingen komen vaak voor bij ouderen, ook zonder dementie. Toch zijn er in toenemende mate aanwijzingen dat deze afwijkingen een rol spelen bij cognitieve achteruitgang, tot aan dementie toe. Intellectuele achteruitgang bij ouderen komt vaak voor en heeft daardoor enorme gevolgen voor de gezondheidszorg in zijn algemeen, vooral in een vergrijzende samenleving als de onze, en voor de patiënt en zijn of haar familie in het bijzonder. Vroege detectie van mensen die een verhoogd risico hebben voor cognitieve achteruitgang of dementie zou mogelijkheden kunnen bieden voor vroege interventie en mogelijke behandeling van deze ziekten. De vraagstelling van dit proefschrift was een nadere bestudering van de risicofactoren voor witte stofafwijkingen, met nadruk op de tijdsfactor, binnen een gezonde, niet demente, populatie ouderen. Dit onderzoek werd uitgevoerd binnen de Rotterdam Scan Study.

De Rotterdam Scan Study bestudeert determinanten en gevolgen van hersenveranderingen bij ouderen. Van 1995 tot 1996 werden 1904 mensen tussen de 60 en de 90 jaar uitgenodigd. Deze mensen werden geworven uit de twee verschillende prospectieve bevolkingsonderzoeken, namelijk de Rotterdam Study (in het Nederlands: het Erasmus Rotterdam Gezondheid en Ouderen (ERGO) onderzoek) en het Epidemiologisch Preventief Onderzoek Zoetermeer (EPOZ). Van de 1904 mensen bestonden er bij 1724 geen contra-indicaties voor het MRI-onderzoek van de hersenenen; 1084 mensen deden dat ook daadwerkelijk (respons 63%). De EPOZ studie is reeds begonnen tussen 1975 en 1978, onder 10361 mensen tussen de 5 en de 91 jaar, met als doel het bestuderen van determinanten van chronische ziekten. Door deze lange follow-up (ongeveer 20 jaar) kunnen we het verband in de tijd bestuderen tussen een risicofactor die al relatief vroeg in het leven aanwezig was, en witte stofafwijkingen later in het leven. Het ERGO onderzoek (start 1990-1993) omvat 7983 ouderen van 55 jaar en ouder en onderzoekt risicofactoren voor neurologische, oogheelkundige, cardiovasculaire ziekten en voor ziekten van het bewegingsapparaat. Dit stelt ons in staat om het verband na te gaan tussen risicofactoren relatief laat in het leven en de aanwezigheid van witte stofafwijkingen enkele jaren later (ongeveer 5 jaar).

Voor de Rotterdam Scan Study werd een speciale beoordelingsmethode voor witte stofafwijkingen ontworpen, waarbij onderscheid werd gemaakt tussen afwijkingen in de subcorticale witte stof, en de periventriculaire (rond de ventrikels) witte stof.

Hoofdstuk 2.1 geeft een overzicht van de literatuur over de risicofactoren voor witte stofafwijkingen en hun frequentie, terwijl **hoofdstuk 2.2** de geslachts -en leeftijdsspecifieke frequentieverdeling van witte

stofafwijkingen in de Rotterdam Scan Study beschrijft. Er was een significante relatie tussen leeftijd en de aanwezigheid van witte stofafwijkingen. Wij vonden tevens dat vrouwen vaker en meer witte stofafwijkingen hadden dan mannen, met name in het frontale deel van de hersenen.

Hoofdstuk 3 beschrijft het verband tussen bloeddruk en witte stofafwijkingen. Er zijn aanwijzingen dat een verandering van de bloeddruk een betere voorspeller is voor hart -en vaatziekten dan de absolute waarde van de bloeddruk. In overeenstemming hiermee zijn bevindingen in sommige andere studies bij ouderen, die laten zien dat zowel een lage als een hoge bloeddruk het risico voor cardiovasculaire aandoeningen verhoogt. **Hoofdstuk 3.1** beschrijft de relatie tussen bloeddruk, bloeddruk veranderingen en witte stofafwijkingen. Mensen bij wie zich in 20 jaar een aanzienlijke afname of stijging van hun diastolische bloeddruk had had voorgedaan, hadden een ongeveer twee maal zo hoog risico voor zowel sucorticale als periventriculaire witte stofafwijkingen. Dit zogenaamde J-vormige verband vonden we ook in de relatie tussen diastolische bloeddruk en witte stofafwijkingen bij mensen die al eens een hartinfarct hadden doorgemaakt. Voor systolische bloeddruk was het verband tussen vroegere bloeddruk en huidige afwijkingen van de witte stof lineair, zowel bij mensen met als zonder een doorgemaakt hartinfarct. In **hoofdstuk 3.2** wordt het verband tussen hypertensie en witte stofafwijkingen beschreven. De relatie tussen een risicofactor die eveneens geassocieerd is met een verhoogd risico op overlijden en bijvoorbeeld witte stofafwijkingen kan worden vertekent door selectieve overleving van mensen zonder de risicofactor. Wij vonden dat dit mogelijk ook in ons onderzoek van invloed was en vonden dat dit het minst van belang was bij deelnemers die tijdens ons onderzoek tussen de 60 en de 70 jaar waren. In deze leeftijdsgroep vonden we een zestien tot twintig keer verhoogd risico voor periventriculaire of subcorticale witte stofafwijkingen bij diegenen met ruim 20 jaar hypertensie. Tevens maakten we aannemelijk dat effectieve behandeling van hypertensie het risico op witte stofafwijkingen verlaagt.

Hoofdstuk 4 is gewijd aan het verband tussen atherosclerose en witte stofafwijkingen. **Hoofdstuk 4.1** gaat over de relatie tussen atherosclerose in de abdominale aorta en witte stofafwijkingen. Mensen die al atherosclerose in de aorta hadden gedurende middelbare leeftijd hadden een tweeënhalf maal verhoogd risico op periventriculaire witte stofafwijkingen 20 jaar later, terwijl er geen verband was met subcorticale witte stofafwijkingen. Er was daarentegen geen relatie tussen atherosclerose van de aorta gemeten laat in het leven en witte stofafwijkingen. **Hoofdstuk 4.2** beschrijft een gevonden verband tussen atherosclerose in de halsslagader en periventriculaire witte stofafwijkingen, terwijl dit niet

gevonden voor subcorticale witte stofafwijkingen. Mensen met perifeer vaatlijden hadden een licht verhoogd volume aan subcorticale witte stofafwijkingen, terwijl er voor de periventriculaire afwijkingen geen verschil was. **Hoofdstuk 4.3** beschrijft het verband tussen atriumfibrilleren en witte stofafwijkingen. Mensen met atriumfibrilleren hadden een tweemaal verhoogd risico voor periventriculaire witte stofafwijkingen, terwijl er geen relatie was voor subcorticale witte stofafwijkingen. Er bleek een kleine groep mensen te zijn met atriumfibrillleren *en* linker ventrikel hypertrofie, die een zeven maal verhoogd risico hadden voor periventriculaire witte stofafwijkingen (en niet voor subcorticale afwijkingen). Op grond van deze resultaten kan men veronderstellen dat cerebrale hypoperfusie de meest waarschijnlijke intermediaire factor was bij het ontstaan van de witte stofafwijkingen, en niet eventuele, door atriumfibrilleren gevormde, thromboembolieën. Deze associatie kan mogelijk het door anderen gevonden verband tussen atriumfibrilleren en dementie verklaren. Onder normale omstandigheden kunnen arteriolae in de hersenen verwijden onder invloed van stimuli als kooldioxide of een daling van de bloeddruk (chemoregulatie resp. autoregulatie), om een zo contstant mogelijke cerebrale doorbloeding te bewerkstelligen. Atherosclerose kan deze functie van de wand van de arteriolae aantasten en zo leiden tot een verminderde cerebrale perfusie. Inderdaad vonden wij bij mensen met een goede vasomotoire reserve capaciteit (na toediening van kooldioxide) een significant verlaagd risico voor periventriculaire en subcorticale witte stofafwijkingen (**hoofdstuk 4.4**).

Ten slotte onderzochten we in **hoofdstuk 5** het verband tussen het apolipoproteine E genotype (APOE) en witte stofafwijkingen. Eerdere onderzoekingen lieten een verband zien tussen het APOE*4 genotype en dementie. Er wordt wel verondersteld dat witte stofafwijkingen de intermediaire factor vormen. Wij vonden een zevenmaal resp. tweemaal verhoogd risico voor periventriculaire of subcorticale witte stofafwijkingen bij dragers van het APOE2E4 genotype, vergeleken met dragers van het APOE3E3 genotype. Mensen met het APOE*4 genotype hadden een, bijna significant, anderhalf keer verhoogd risico voor beide typen witte stofafwijkingen.

In **hoofdstuk 6** worden de bevindingen van ons onderzoek bezien in samenhang met andere studies. Tevens wordt een verklaring voorgesteld voor het ontstaan van witte stofafwijkingen. Wij vonden dat de prevalentie van witte stofafwijkingen hoog was en dat er een sterk verband bestond met de klassieke cardiovasculaire risicofactoren zoals hypertensie en atherosclerose. Onze resultaten laten zien dat het mogelijk en belangrijk is om mensen met een verhoogd risico reeds vroeg in het leven op te sporen, zodat preventie en eventueel behandeling nog goed mogelijk zijn.

Onze veronderstelling over de ontstaanswijze van witte stofafwijkingen is als volgt: langdurige hypertensie leidt tot atherosclerotische veranderingen in de kleine cerebrale arteriolen. Deze vaatwandveranderingen verhinderen mogelijk een doeltreffende reactie op een afnemende cerebrale doorbloeding, hetgeen leidt tot chronische ischemie. De ischemische veranderingen van de witte stof leiden waarschijnlijk tot het typische MRI-beeld van witte stofafwijkingen.

Er zijn nu meer en meer aanwijzingen voor een verband tussen witte stofafwijkingen enerzijds en cognitieve achteruitgang en dementie en depressie anderzijds op oudere leeftijd. Uit onze bevindingen blijkt dat te beïnvloeden vasculaire factoren de kans op witte stofafwijkingen sterk verhogen. In een gerandomiseerde klinische trial zou het effect kunnen worden onderzocht van behandeling van hypertensie en atriumfibrilleren op witte stofafwijkingen en de daarmee gepaard gaande cognitieve stoornissen. Vanuit het oogpunt van efficiency en vanwege ethische bezwaren zou een dergelijke trial bij voorkeur moeten worden uitgevoerd binnen het kader van een trial die is gericht op de meest ernstige complicaties van bovengenoemde risicofactoren (hartinfarcten en beroertes).

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About the author

The author of this thesis was born on July 12, 1969 in Zwolle. He attended secondary school at the Carolus Clusius College in the same place and he passed his exam in 1987. That year he started his studies medical biology at Utrecht University. During this study he performed a 7.5 months period of practical work on thymic innervation (Dr. H.J. Schuurman, Department of Pathology, University Hospital Utrecht) and a 10 months period of practical work on the $GABA_A$-receptor function during cerebral ischemia in a rat model (Prof. dr C.A.F. Tulleken, Department of Neurosurgery, University Hospital Utrecht and Prof. dr F.H.Lopes da Silva, Department of Experimental Zoology, University of Amsterdam). In addition he was a student assistant in pathology in 1991. In 1991 he started his medical studies at the Utrecht University, during which he performed a 5 month period of practical work on mRNA editing of the glutamate receptor during cerebral ischemia in a rat model (Prof. dr F.H.Lopes da Silva, Department of Experimental Zoology, University of Amsterdam). In 1993 he graduated from medical biology. He got his Medical Degree in October 1995. In the same month he started the research project as described in this thesis and started his epidemiology training (MSc Clinical Epidemiology, June 1998) at the Department of Epidemiology & Biostatistics (head: Prof. dr A. Hofman). From January 1, 1999 he started his training as a neurologist at the Department of Neurology at the University Hospital Utrecht (head: Prof. dr J. van Gijn).