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From normal aging to dementia:

Risk factors & clinical findings in relation to vascular changes on brain MRI

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VRIJE UNIVERSITEIT

From normal aging to dementia: Risk factors & clinical findings in relation to vascular changes on brain MRI

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Geneeskunde
op woensdag 23 december 2009 om 15.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Salka Sterre Staekenborg

geboren te Utrecht

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copromotor:	dr. W.M. van der Flier

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Contents

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Part 1

General introduction

Poetische overpeinzing

Nihil durare potest tempore perpetuo.
Niets kan voor immer en altijd duren.

Cum bene sol nituit, redditur oceano.
Als de zon goed heeft geschenen, zinkt ze weg in de zee.

Descrescit Phoebe, qua modo plena fuit.
Phoebe, die net nog vol was, neemt in omvang af.

Ventorum feritas saepe fit aura levis.
De wilde wind wordt vaak een zachte zucht.

In steen gebeitelde inscriptie gevonden in Pompeï (C.I.L. IV, 9123)
Uit: Op de muren van Pompeji, Uitgeverij Ambo bv Baarn, 1993

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Introduction

As the baby boomers reach seniority and life expectancy increases, the number of elderly is growing, and will keep rising in the future. As a consequence of the aging population the prevalence of certain diseases, like cardiovascular disease and dementia, increases as well. The number of patients with dementia in Europe is estimated to rise over 16 million within 50 years.[1] In addition, in the Netherlands - comparable to most western countries - both cardiovascular disease and dementia rank in the top five of diseases with highest mortality.[2]

The adult human brain accounts for only about 2% of the body weight but it receives about 20% of the cardiac output.[3] It is obvious that heart and brain are related to each other, and that insufficiency in blood supply may lead to essential damage of the brain. Therefore, blood flow to, and in the brain are securely controlled. On the other hand, vascular disease is highly prevalent in elderly, such as atherosclerosis and a diminished heart function, and ultimately these diseases may have its consequences on the blood flow in the brain. Pathological brain studies showed that in elderly the prevalence of cerebrovascular pathology is extremely high (78%).[4] Alzheimer pathology was also commonly found (70%), and interestingly, in brains of patients with clinical features of dementia often a co-existence of both Alzheimer pathology and cerebrovascular pathology has been demonstrated.[4,5] A valuable method to visualize and examine the presence of cerebrovascular disease in vivo is with the use of magnetic resonance imaging (MRI) of the brain.

Vascular measures on brain MRI

MRI can be used in different ways to examine cerebrovascular function and disease. Blood flow to the brain can be investigated with the use of two-dimensional (2D) phase-contrast MRI. Herewith the blood flow in both carotid arteries and the basilar artery can be determined and subsequently, total blood flow to the brain can be calculated (see figure 1). The method has proven to be fast and accurate, but it must be noted that it is not the same as determination of regional cerebral blood flow which is measured at brain tissue level (e.g. as with positron emission tomography).[6]

Furthermore, structural MRI can be used to demonstrate the presence of large vessel and small vessel disease. Large vessel disease includes cortical infarcts in the territory of large blood vessels (figure 2). Important expressions of small vessel disease include white matter hyperintensities (WMH), lacunes and microbleeds (figure 3). WMH are commonly defined on T2-weighted MRI scans, such as FLAIR images. The severity of WMH can be assessed using visual rating scales as the Fazekas scale and the Scheltens scale, or using more sophisticated automatic methods to measure volumes of WMH.[7-9] Lacunes are identified as small cavities surrounded by white matter or subcortical grey matter with a minimum diameter of 3mm. The signal intensities are comparable to cerebrospinal fluid on all sequences (on T1-hypointense and T2-hyperintense). Microbleeds are defined as strongly hypointense, mostly round lesions on the axial FLASH 2D images with a diameter between 2 and 10mm.

In line with neuropathological findings, cerebrovascular abnormalities on MRI are commonly found in elderly.[10] Moreover, the prevalence of vascular disease on brain MRI has been reported to be higher in patients with dementia, although the clinical implications are not entirely clear.[11-13]

Dementia

Dementia is characterized by an acquired impairment of cognitive function in at least two domains, which interferes with normal social or occupational performance (and is not attributable to delirium or psychiatric disorders).[14] The most common type of dementia is Alzheimer's disease (AD), followed by vascular dementia (VaD). AD, typically presents with severe memory impairment along with other cognitive deficits, is currently diagnosed by the criteria of the National Institute on Neurological and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA; table 1).[15] The disease is named after the German neuropathologist, Alois Alzheimer, who reported already in 1906 on a patient, named as we now know Auguste D (her initials AD foretold the future!) who at neuropathology showed the histopathological characteristics of what is nowadays

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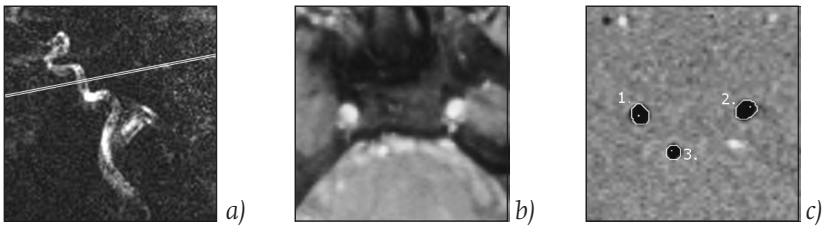

Figure 1;
Total cerebral blood flow measurement using 2D phase-contrast MRI. a) Sagittal 2D phase contrast MRI angiographic scout image for localization of the phase-contrast imaging plane (white line) b) anatomical view of transverse image perpendicular to the carotid and the basilar arteries c) 2D gradient-echo phase contrast sequence on which the blood vessels are identified after which delineation of the vessel is drawn (1: right carotid artery, 2: left carotid artery, 3: basilar artery).

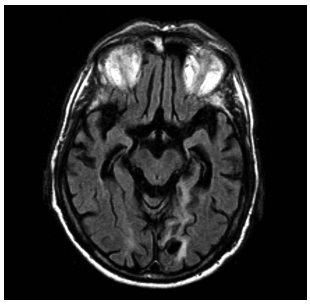

Figure 2;
Axial FLAIR image showing an example of a large vessel infarct of the inferior medial temporal lobe on the left side.

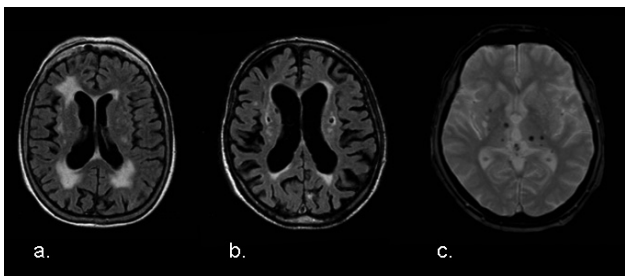

Figure 3;
Examples of MRI expressions of small vessel disease:
a) axial FLAIR image showing confluent white matter hyperintensities
b) axial FLAIR image showing two lacunes in the right hemisphere and one lacune in the left hemisphere
c) axial FLASH 2D image showing microbleeds in the basal ganglia/thalamus.

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Table 1; NINDCDS-ADRDA criteria for probable Alzheimer's disease[15]

1. Dementia established by clinical examination and confirmed by neuropsychological tests
2. Deficits in two or more areas of cognition, including memory impairment
3. Progressive worsening of memory and other cognitive functions
4. No disturbances of consciousness
5. Onset between ages 40 and 90
6. Absence of systemic disorders or other brain disease that in and of themselves could account for the progressive deficits in memory and cognition

recognized as AD (amyloid plaques and neurofibrillary tangles).[16] Less known is the fact that Alois Alzheimer wrote many more papers on VaD, including a detailed description of what was later to become Binswanger's Disease, that Otto Binswanger had only described macroscopically, and recognized the importance of cerebrovascular disease in relation to certain neuropsychiatric conditions.[17]

Vascular dementia

Traditionally, VaD has been recognized to develop after multiple strokes. The name 'multi-infarct dementia' became synonymous with all dementias of vascular origin, incorrectly implying that multiple brain infarcts are the only cause of VaD, not recognising small vessel disease and strategic small infarcts. The experience learns that VaD is difficult to define, leading to several different criteria that are in use in different centres over the world. At present, the criteria of the National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et al'Enseignement en Neurosciences (NINDS-AIREN) are the diagnostic criteria which are most often used in VaD studies.[18] These criteria require the presence of dementia, defined as cognitive decline in memory and 2 other domains, with interference in activities of daily living, and evidence of cerebrovascular disease. The latter includes both proof on brain imaging and the presence of focal signs on neurological examination (table 2). Most likely due to the stringent clinical and radiological definitions the group of VaD patients has hardly been examined compared to patients with other dementias, like AD, with regard to risk factor profiles and clinical features.

Mild cognitive impairment

It is thought that dementia develops gradually and in a certain number of patients is preceded by cognitive impairment not sufficient for the diagnosis of dementia – a stage usually referred to as mild cognitive impairment (MCI).[19] It is increasingly recognized that the group of MCI patients is very heterogeneous: MCI patients have an increased risk of progression to dementia, mostly AD, but some will develop other types of dementia, whereas others will remain stable. Atrophy of the brain, especially of the medial temporal lobe has been shown to be a powerful and independent predictor of progression to dementia in MCI patients.[20-22] In contrast to atrophy, the impact of cerebrovascular disease on progression to dementia in this patient group has not been clarified.

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Table 2; NINDS-AIREN criteria for probable vascular dementia[18]

1. Dementia
Defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more domains, preferably established by clinical examination and documented by neuropsychological testing;
Deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.
2. Cerebrovascular disease
Defined by the presence of focal signs on neurologic examination, such as hemiparesis and Babinski sign, consistent with stroke (with or without history of stroke);
evidence of relevant cerebrovascular disease by brain imaging (CT or MRI).
3. A relationship between the above two disorders
Manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

Clinical picture

By definition the most prominent clinical feature of dementia is cognitive impairment; especially compromised memory, along with other domains like orientation, attention, language, executive functions, praxis and visuospatial functions. However, as certain brain functions diminish, also other clinical signs may develop.

There is some literature about a higher prevalence of physical neurological signs, like extrapyramidal signs in AD, but the number of reports is limited and often includes small study populations. Current criteria of VaD require the presence of focal neurological signs, but in fact which signs are exhibited in relation to what kind of cerebrovascular damage has not been established in VaD patients.[18] Moreover, the origin of neurological signs in dementia is unclear. It is not known whether these signs reflect age-associated changes, if they are the result of degenerative abnormalities, or if vascular pathology plays a role.

Next to cognitive impairment and neurological signs, behavioural and psychological symptoms are important in dementia.[23] For example according to Alzheimer's description of Auguste D., she would have suffered next to amnesia and disorientation, from depression, hallucinations and jealousy towards her husband.[16] Behavioural and psychological symptoms in dementia have been shown to be associated with worse prognosis, higher cost of care, earlier institutionalisation and increased caregiver burden.[24] Therefore it is remarkable that literature on the prevalence of these symptoms and their radiological underpinnings is scarce.

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Aims of the thesis

The general objective of this thesis was to explore different vascular MRI measures, like total cerebral blood flow, large vessel disease and small vessel disease, in the clinical spectrum from normal aging to dementia and to seek relations with possible risk factors. Additionally, we aimed to get a better view of the clinical picture of dementia, with regard to the presence of neurological signs and behavioural and psychological symptoms, and sought to determine possible associations with MRI measures.

Thesis outline

Cerebral blood flow in elderly

First, we aimed to get a better view of associations between both cardiovascular risk factors and brain characteristics, and total cerebral blood flow at old age. In **chapter 2** we describe two studies on total blood flow to the brain in a population based cohort elderly. The studies were performed as part of the Age, Gene/Environment Susceptibility–Reykjavik Study (AGES-Reykjavik).[25] In **chapter 2.1** we report the results of analyses of a wide spectrum of cardiovascular characteristics assessed both at mid-life and late-life in association to total cerebral blood flow in 822 elderly participants. In **chapter 2.2** we calculated total brain perfusion (total cerebral blood flow per 100mL brain volume) for a sub group, and examined the cross-sectional relation between brain volumes and total cerebral blood flow and total brain perfusion. Subsequently, we determined annualized measures of grey matter atrophy, whole-brain atrophy and progression of WMH and aimed to learn whether these measures were related to a lower total cerebral blood flow and lower total brain perfusion at follow-up.

Vascular MRI measures in mild cognitive impairment and dementia

Then, we shifted to a population of patients with cognitive deficits, and examined the role of cerebrovascular disease on MRI in patients with cognitive impairment not sufficient for the diagnosis of dementia. MCI patients were followed for 2 years and we sought to determine associations between presence of baseline atrophy and cerebrovascular disease and progression to dementia (**chapter 3.1**). In **chapter 3.2** we investigated the baseline characteristics of a large cohort of patients with VaD who participated in a multicenter treatment trial (the VantagE study). To understand more about this type of dementia we compared patients with small vessel disease (lacunes and WMH) and large vessel disease (large territorial or strategical infarcts) according to their clinical and MRI characteristics and risk factor profiles.

Neurological signs in dementia and associations with MRI measures

In the last sections of this thesis we took a closer look at the clinical sequelae outside of dementia. **Chapter 4.1** describes the prevalence of extrapyramidal signs and unilateral signs in a large cohort of patients attending a memory clinic, where we expected to find a higher prevalence of signs in patients with dementia compared to non-demented subjects. Secondly, we determined presence of WMH in this population and studied whether patients with extrapyramidal signs or unilateral signs showed a larger volume of WMH, hypothesizing that ischemic vascular damage plays a role in the presence of these signs in dementia. **Chapter 4.2** focuses on the prevalence of a number of neurological signs in a large population of patients with VaD, additionally aiming to determine if the relative frequency of specific neurological signs depends on type of cerebrovascular disease on MRI.

Neuropsychiatric symptoms in Alzheimer's disease and vascular dementia and associations with MRI measures

In **chapter 5.1** we describe the prevalence of behavioural and psychological symptoms in patients with AD and investigated differences in prevalence of these symptoms according to the presence of medial temporal lobe atrophy and WMH on MRI. Subsequently, behavioural and psychological symptoms were investigated in VaD. Severity and relative frequency of symptoms was compared between small vessel VaD and large vessel VaD (**chapter 5.2**).

In **chapter 6** the main findings of this thesis are summarized, followed by a discussion of the results and recommendations for future directions.

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Part 2

Cerebral blood flow in elderly

Bí, bí og blaka

Bí, bí og blaka,

álftirnar kvaka,

ég læt sem ég sofi,

en samt mun ég vaka.

Bíum bíum bamba,

börnin litlu ramba

fram um fjalla kamba

ao leita sér lamba.

Icelandic lullaby, written by Sveinbjörn Egilsson (1791 - 1852),
and sang by my grandmother before we went to sleep

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2.1 Mid-life and late-life cardiovascular characteristics and total cerebral blood flow; the AGES-Reykjavik study

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Abstract

Background

By middle age brain pathology leading to cognitive impairment has already started. One indicator of pathology is a decline of total blood flow to the brain (tCBF). Mid- and late-life cardiovascular factors may contribute to the reduction in tCBF. We assess the association of mid- and late-life cardiovascular factors measured 30 and 5 yrs prior to the measure of tCBF.

Methods

tCBF was measured with two-dimensional phase-contrast MR angiography in 822 men and women (58% women, mean age 79 yrs) who participated in the Reykjavik Study (mid-life) and its follow on, the AGES-Reykjavik Study I (late-life) and II (measure of tCBF). We used linear regression analysis to study the association of tCBF to cardiovascular characteristics measured in mid- and late-life, adjusting for age, sex MRI detected infarcts, and brain volume.

Results

Mean(SD) tCBF was 578(108) mL/min, increased with age and did not differ by sex. There were statistically significant ($p<0.05$) inverse associations of tCBF to both mid- and late-life measures of hemoglobin, hematocrit and diastolic blood pressure, and to late-life indicators of major ECG detected coronary abnormalitites.

Interpretation

Hemotologic, hemodynamic and cardiac characteristics affecting cardiac output and amount of blood flow to the brain measured at mid-life and at late-life, were associated with lower tCBF in late-life.

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Introduction

The adult human brain accounts for approximately 2% of body weight but it receives about 20% of the cardiac output.[1] Because of the brain's vital need for a continuous supply of oxygen and glucose, cerebral blood flow (CBF) must be tightly regulated. Normally, the brain alters regional blood flow in response to changes in brain activity, while maintaining a relatively constant overall CBF.[1] However, total cerebral blood flow (tCBF) to the brain, determined by summing the flow in both carotid arteries and the basilar artery, is known to decline with increasing age.[2] TCBF is related to brain size, and a reduction of brain volume with ageing (i.e. due to processes such as neurodegeneration) may be the cause of a lower tCBF in elderly.[3] However, blood oxygenation, rheology, hemodynamics, cardiac function, and other cardiovascular factors might also play important roles in this decline with age.

tCBF can be measured in several ways. At brain tissue level, regional CBF per 100g brain tissue per minute can be determined using techniques such as positron emission tomography, single photon emission computed tomography, and xenon-computed tomography. However, these measurements are complex and invasive and are difficult to implement in studies of the general population. More recently, two-dimensional (2D) phase-contrast MR angiography.[4] has been shown to be a non-invasive, fast and accurate measure of tCBF.

The first large studies on tCBF and vascular risk factors using 2D phase-contrast imaging have been recently published.[3, 5, 6] The results differ slightly, but in general, the studies report inverse relations of tCBF to hypertension, diabetes, increasing BMI, and a history of cerebrovascular disease.[3, 5, 6] However, one study sample consisted of subjects with symptomatic vascular disease and a mean age of 58yrs.[5, 6] The other study was population based and investigated vascular risk factors in a sample mean age 68yrs old.[3]

We were interested in tCBF and relations with cardiovascular determinants in an older population since this is the group with the greatest prevalence of cognitive dysfunction and brain atrophy. Furthermore, because it is increasingly recognized risk factors measured in mid-life are associated with late-life brain pathology, we investigated whether tCBF in late-life is related to cardiovascular risk factors earlier in life. The AGES-Reykjavik study is a single center population-based follow-up of members of the Reykjavik study, a study initiated in 1967 by the Icelandic Heart Association to investigate cardiovascular disease and risk factors.[7, 8] This provided the unique possibility to examine tCBF in a large population based cohort and to determine the associations between tCBF and a wide spectrum of cardiovascular factors assessed both at mid-life and late-life.

Methods

Study population

The design of the Age, Gene/Environment Susceptibility–Reykjavik Study (AGES-Reykjavik) has been described previously.[7] As noted, AGES-Reykjavik originates from the Reykjavik Study, a community-based cohort established in 1967 to prospectively study cardiovascular disease in Iceland. Between 2002 and 2006, 5764 participants were examined (visit I). In November 2006 follow-up assessments started (and are ongoing) (visit II). AGES-Reykjavik was approved by the National Bioethics Committee in Iceland, which acts as the institutional review board for the Icelandic Heart Association (approval number VSN-00-063), and by the institutional review board serving the National Institute on Aging Intramural Research Program. All participants gave written informed consent.

MRI measures

MRI of the brain was performed at visits I and II using the same protocols and machine. The visit II exam also included a 2D phase-contrast sequence necessary for tCBF determination. In this analysis we included all subjects who underwent brain MRI at visit II from May 2006 to September 2008 (n=876).

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MRI protocol

MRI was performed on a 1.5 Tesla machine (General Electric Medical Systems, Waukesha, Wisconsin, USA) following a standard protocol, including a PD/T2w FSE sequence (proton density/T2-weighted fast spin echo; field of view [FOV] 220mm, matrix 256x256, slice thickness 3.0mm, echo time [TE] 22ms, TE 90ms, repetition time [TR]: 3220ms, echo train length 8, flip angle 90°) and a FLAIR sequence (fluid attenuated inversion recovery; FOV 220mm, matrix 256x256, slice thickness: 3mm, TE: 100ms, TR: 8000ms, inversion time [TI] 2200ms, flip angle 90°). Additionally, images were acquired with a T1-weighted three-dimensional spoiled gradient echo sequence (FOV 240mm, matrix 256x256, slice thickness 1.5mm, TE 8ms, TR 21ms, flip angle 30°). All images were acquired to give full brain coverage. Slices were angled parallel to the anterior commisure-posterior comissure line to give reproducibility image views in the oblique-axial plane.

The 2D phase-contrast scan protocol included the following: First, a sagittal 2D phase-contrast MRI angiographic scout image was acquired (FOV 220mm, matrix 256x256, TE 6.1ms, TR 33ms, flip angle 30º, velocity encoding 80cm/sec, slice thickness 60mm (Figure 1a). On this scout image, an oblique transverse imaging plane perpendicular to the ICAs and the BA was chosen for a 2D gradient-echo phase- contrast sequence (FOV 220mm, matrix 256x256, TE 6.2ms, TR 20ms, flip angle 9°, velocity encoding 100cm/sec, slice thickness 5mm).

Analysis of total cerebral blood flow (visit II)

The images of the cerebral blood flow were analyzed with the software package FLOW (Division of Image Processing, Department of Radiology, Leiden University Medical Center).9 This software provides automated detection of the vessel lumen boundaries and subsequent quantification of flow and velocities (Figure 1b and 1c). The only user-interaction required is the manual placement of a seed point in each of the vessels to be analyzed. All determinations were performed by the same person, with an excellent agreement between repeated blood flow measurements of 20 scans (coefficient of variation 1.7%). The resultant value of the mean signal intensity in each vessel represented the spatial- and time averaged flow velocity in that vessel, which is expressed in centimeters per second. By multiplying this average velocity by the cross sectional area of the pixels in the vessel, the flow rate (in mL/s) of the carotid arteries and basilar artery can be calculated. tCBF is calculated by summing the flow rates of the carotid arteries and the basilar artery and multiplied by 60 sec/min. As representation of stationary tissue, ideally the velocity measured in background tissue should be zero. However, the flow sequences had some offset velocity (likely inherent to the scanner and the methodology). Therefore, a fourth region of interest (ROI) was drawn in the pons, and the average velocity in this fourth ROI was subtracted to correct for the velocity offset (median [min-max] 1.0 [0.2-1.5] cm/sec).

Assessmentof covarying brain characteristics

Brain volume, an important determinant of tCBF,3 was determined from visit 1 MRI's. Volumes of grey matter, white matter, white matter hyperintensity (WMH) and cerebrospinal fluid were computed automatically with an algorithm based on the Montreal Neurological Institute (MNI) pipeline.10
The AGES-Reykjavik/MNI pipeline has been modified to accommodate full brain coverage including cerebellum and brain stem, multi-spectral analysis using T1-weighted 3D SPGR, FLAIR and PD/T2-weighted FSE images, high throughput, automatic skull removal and minimal editing. Total brain volume was determined by summing the volumes of the grey matter, white matter and WMH; this was standardized by total intracranial volume, giving a percent. Cerebral infarcts, which may also influence blood flow, were defined as parenchymal defects, areas isointense to cerebral spinal fluid on all pulse sequences with a minimum diameter of 4mm.

Assessment of cardiovascular factors

Mid-life

Mid-life data on cardiovascular factors were collected as part of the Reykjavik Study.8 Participants answered a standardized questionnaire, underwent a clinical exam, had blood drawn and an X-ray and electrocardiogram (ECG) made. We examined risk factors, classified into 4 groups: hemotologic, hemodynamic, metabolic and cardiac factors. The individual variables were measured as follows:

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1) Hematologic factors: hemoglobin (mmol/L) and hematocrit (L/L). 2) Hemodynamic factors: diastolic and systolic blood pressure (mm/Hg –mean value of two measurements on the right arm in supine position), pulse pressure (systolic – diastolic blood pressure), mean arterial pressure (MAP; 1/3 systolic + 2/3 diastolic blood pressure), and hypertension (reported history of hypertension, reported use of anti-hypertensive medication, a systolic blood pressure ≥140mmHg or a diastolic blood pressure of ≥90mmHg, coded as yes/no; 3) Metabolic factors: serum fasting glucose (mmol/L); total cholesterol (mmol/L), and triglycerides (mmol/L) and body mass index (BMI)(kg/m2); 4) Coronary factors: current smoking (yes/no), a history of cardiac disease (defined by history of angina pectoris, heart disease, heart valve disease or coronary thrombosis, coded as yes/no), presence of left ventricular hypertrophy on chest X-ray (yes/no); any cardiac disease visible on X-ray (defined by presence of left ventricular hypertrophy, right ventricular hypertrophy, mitral valve defect or calcium in the aorta (yes/no)), and minor and major abnormalities on a 12 lead ECG, coded on the basis of the Minnesota coding criteria.[11] To obtain groups sufficiently large to allow reliable conclusions, ECG findings were further pooled using the criteria of the pooling project.[12] Minor ECG abnormalities included borderline Q wave (Minnesota code I3), left or right axis deviation (codes II1-2), QRS high voltage (codes III1-2), borderline ST segment depression (code IV4) T wave flatting (code V3), and QRS low voltage (code IX1). Major ECG abnormalities consisted of ST segment depression (codes IV1-2), T wave inversion (codes V1-2), complete or second degree atrioventricular block (codes VI1-2), complete left or right bundle branch block (codes VII1-2), frequent premature beats (code VIII1) and atrial fibrillation or flutter (code VIII3).

Late-life

Participants answered a questionnaire, had their medication registered based on vials they brought to the exam, had clinical measures made, a fasting blood sample drawn, and underwent extensive bio-imaging. The following variables were included in the analyses, which, when relevant, were defined in the same way as the mid-life variables: 1) Hematologic factors: hemoglobin (mmol/L) and hematocrit (L/L); Hemodynamic factors: diastolic and systolic blood pressure; pulse pressure; and hypertension; 3) Metabolic factors: fasting glucose (mmol/L), total cholesterol (mmol/L), triglycerides (mmol/L), BMI (kg/m2), and diabetes (defined as history of diabetes, using oral hypoglycemic medication or insulin, or if fasting plasma glucose was ≥7.0mmol/L (≥126mg/dL)); 4) Coronary factors: current smoking (yes/no), a history of cardiac disease (defined as a history of congestive heart disease, heart valve disorder, angina/myocardial infarction or CABG, coded as yes/no); a history of TIA or stroke (yes/no), presence of atherosclerosis determined by coronary artery calcium load (quantified with computed tomographic images and expressed in Agatston units); minor abnormalities (yes/no) and major abnormalities (yes/no) on ECG following the same classification as at mid-life.

Analysis

Analytical sample

TCBF was measured in n=876 subjects. We excluded 14 subjects due to incorrect tCBF measurements, 7 due to missing mid-life data, and 33 subjects due to missing brain volume data. This resulted in a sample of 822 available for this study, with a mean(SD) age of 79(5) yrs at time of blood flow determination, 74(5) yrs at assessment of late-life life cardiovascular factors, and a mean(SD) age of 49(6) yrs at assessment of mid-life cardiovascular factors. Excluded subjects did not differ in sex, but were slightly older compared to the rest of the sample (mean [SD] age 82[6] yrs versus 79[5] yrs).

Statistical analysis

Statistical analyses were performed using SPSS 15.0 for Windows (SPSS Inc). We investigated the association of tCBF (dependent) to mid- (and late-) life cardiovascular determinants with linear regression analyses. Two models were estimated: model 1, adjusted for age and sex, and model 2, adjusted for age, sex, presence of infarct on MRI, and brain volume. Coronary artery calcium expressed in Agatston units was not normally distributed, therefore we transformed the variable with the natural log and added 1 to avoid zeros (ln [1+ coronary artery calcium).

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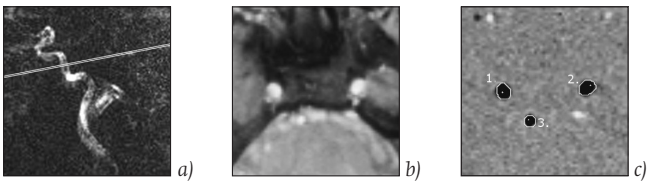

Figure 1;
Total cerebral blood flow measurement using 2D phase-contrast MRI. a) Sagittal 2D phase contrast MRI angiographic scout image for localization of the phase-contrast imaging plane (white line) b) anatomical view of transverse image perpendicular to the carotid and the basilar arteries c) 2D gradient-echo phase contrast sequence on which the blood vessels are identified after which delineation of the vessel is drawn (1: right carotid artery, 2: left carotid artery, 3: basilar artery).

Results

The 822 subjects included 479(58%) women. Mean (SD) tCBF was 578(108) mL/min. TCBF decreased as age increased (per sd increase of age, difference in tCBF -4.0 [95% CI:-5.4; -2.6]). Mean (SD) tCBF was lower in women (574 [105] mL/min) compared to men (584 [112] mL/min), but this difference was not statistically significant (p=0.18).

Cardiovascular characteristics at mid-life and late-life (Table 1)

Subjects had slightly higher levels of hemoglobin and hematocrit in mid-life compared to late-life. Only 30% of the subjects had hypertension at mid-life (30%), but by late-life 76% fulfilled criteria for hypertension. Furthermore, compared to late-life, fasting glucose levels were lower at mid-life and diabetes was infrequent. In contrast, in late-life 10% of the sample had diabetes and 8% had a fasting glucose of >7.0 mmol/L. Cardiac disease on ECG was seldom present at mid-life, but at late-life both minor and major ECG abnormalities were observed in one out of five (minor abnormalities 21%, major abnormalities 18%).

Mid-life characteristics and tCBF (Table 2)

Adjusted for age and sex, we found significant inverse relations of tCBF to mid-life hemoglobin, hematocrit and diastolic blood pressure levels. These results remained essentially unchanged after additional adjustment for presence of infarcts and brain volume. In addition, an increase of MAP was associated with a lower tCBF at late-life, independent of age and sex (model 1); but adjustment for brain volume and infarcts (model 2), slightly attenuated the relationship. Other hemodynamic variables (systolic BP, pulse pressure, and hypertension) were not significantly associated with tCBF. Furthermore, adjusted for age and sex, lower tCBF was associated with higher levels of mid-life triglyceride, smoking and the presence of left ventricular hypertrophy on X-ray. However, after adjustment for brain volume and infarcts these associations lost significance.

Late-life characteristics and tCBF (Table 3)

As with the mid-life data, there were strong inverse associations of hemoglobin and hematocrit to tCBF, in the fully adjusted model 2. Similarly, diastolic BP, MAP, and major ECG abnormalities were associated tCBF, independent of age, sex, brain volume and presence of infarcts. Diabetes and increasing levels of fasting glucose levels were significantly associated with lower tCBF, but these associations were markedly reduced after additional adjustment for brain volume and infarcts.

To further explore the hemoglobin associations we stratified subjects into low or high hemoglobin level by the mean hemoglobin level of the sample (low <8.5 mmol/L, high >8.5mmol/L) and we tested for non-linear associations [which were not significant]. Stratification suggested hemoglobin was most strongly associated to lower tCBF in subjects with high hemoglobin levels, compared to subjects with relatively low hemoglobin levels (high hemoglobin: per sd increase of hemoglobin, difference in tCBF -52.6 [95% CI: -73.2;-31.9]; low hemoglobin: per sd increase of hemoglobin, difference in tCBF -20.2 [95% CI: -45.6;5.3].

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Table 1; Cardiovascular factors at mid-life and late life: AGES-Reykjavik Study

n=822 % female n=479 (58%)	Mid-life mean age 49(6) yrs	Late-life mean age 74(5) yrs
Hematologic factors		
Hemoglobin (mmol/L) mean (SD)	8.7 (0.9)	8.5 (0.7)
Hematocrit (L/L) mean (SD)	0.43 (0.04)	0.40 (0.03)
Hemodynamic factors		
Systolic BP (mm/Hg) mean (SD)	130 (15)	141 (19)
Diastolic BP (mm/Hg) mean (SD)	83 (10)	74 (9)
Pulse pressure	47 (9)	66 (17)
Mean arterial pressure	98 (11)	96 (11)
Hypertension n(%)	248 (30%)	627 (76%)
Metabolic factors		
Fasting glucose mean (SD)	4.3 (0.5)	5.8 (1.1)
Fasting glucose >7.0 mmol/L n(%)	0	63 (8%)
Cholesterol (mmol/L) mean (SD)	6.3 (1.1)	5.8 (1.1)
Triglyceride (mmol/L) mean (SD)	1.1 (0.6)	1.2 (0.6)
BMI (kg/m2) mean (SD)	24.7 (3.2)	27.0 (4.0)
Diabetes n(%)	0	81 (10%)
Coronary factors		
Smoking (current) n(%)	308 (38%)	89 (11%)
Self reported history of CHD n(%)	20 (2%)	184 (22%)
Self reported history of stroke/ TIA n(%)	NA	79 (9%)
Coronary artery calcium Ag. units median(interq range)	NA	222 (27-75)
Any cardiac disease visible on X-ray n(%)	74 (9%)	NA
Left ventricular hypertrophy on X-ray n(%)	39 (5%)	NA
Minor abnormalities on ECG n(%)	33 (4%)	171 (21%)
Major abnormalities on ECG n(%)	21 (3%)	146 (18%)

BP = blood pressure; BMI = body mass index; CHD = coronary heart disease; TIA = transient ischemic attack; ECG = electrocardiogram; NA = not ascertained.

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Table 2; Linear regression: mid-life cardiovascular characteristics and tCBF AGES-Reykjavik Study

n=822	Model 1		Model 2	
	B	(95%CI)	B	(95%CI)
Hematologic factors				
Hemoglobin	-16.3*	-28.5;-4.1	-12.7*	-24.2;-1.2
Hematocrit	-4.0*	-6.7;-1.3	-3.0*	-5.6;-0.5
Hemodynamic factors				
Systolic BP	-0.3	-0.7;0.2	-0.05	-0.5;0.4
Diastolic BP	-1.1*	-1.8;-0.3	-0.7	-1.5;0.0
Pulsepressure	0.4	-0.4;1.2	0.6	-0.2,1.3
Mean arterial pressure	-0.7*	-1.4;-0.0	-0.4	1.1,0.3
Hypertension	-14.2	-30.2;1.8	-12.3	-28.2;3.9
Metabolic factors				
Fasting glucose >7.0 mmol/L	-7.3	-23.6;9.1	-6.3	-21.6;9.0
Cholesterol	0.4	-6.6;7.3	0.2	-6.2;6.7
Triglyceride	-17.2*	-30.0;-4.0	-10.4	-22.6;1.7
BMI	-1.5	3.8;0.8	-1.0	-3.1;1.2
Coronary factors				
Current Smoke exposure	-17.9*	-33.6;-2.3	-11.1	-25.9;3.6
Self reported history of CHD	7.9	-39.1;55.0	3.1	-41.0;47.2
Any cardiac disease visible on X-ray	-16.5	-42.5;9.5	-12.0	-36.3;12.4
Left ventricular hypertrophy on X-ray	-34.9*	-69.3;-0.6	-29.6	-61.8;2.6
Minor abnormalities on ECG	-21.0	-58.0;16.1	-13.7	-48.4;21.0
Major abnormalities on ECG	27.9	-18.1;74.0	20.5	-22.7;63.7

Data presented as B or 95% CI. Analysis of data using linear regression models with tCBF (mL/min) as dependent variable and mid-life cardiovascular determinants as independent variable. * p<0.05
BP = blood pressure; BMI = body mass index; CHD = coronary heart disease; ECG = electrocardiogram.
Model 1: adjusted for age and sex
Model 2: additional adjustment for MRI infarct and brain volume

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Table 3; Linear regression: late-life cardiovascular characteristics and tCBF AGES-Reykjavik Study

n=822	Model 1		Model 2	
	B	(95%CI)	B	(95%CI)
Hematologic factors				
Hemoglobin	-47.3*	-58.8;-35.8	-48.7*	-59.4;-38.1
Hematocrit	-10.0*	-12.3;-7.7	-10.0*	-12.2;-7.8
Hemodynamic factors				
Systolic BP	-0.2	-0.5;0.2	-0.1	-0.4;0.3
Diastolic BP	-1.6*	-2.4;-0.8	-1.4*	-2.1;-0.6
Pulse pressure	0.3	-0.2;0.7	0.3	-0.1,0.7
Mean arterial pressure	-0.9*	-1.6;-0.3	-0.7*	-1.4,-0.1
Hypertension	-10.0	-27.5;7.5	-4.1	-20.6;12.3
Metabolic factors				
Fasting glucose >7.0 mmol/L	-29.3*	-56.6;-2.0	-13.1	-38.9;12.7
Total cholesterol	-1.9	-8.7;4.9	-5.1	-11.5;1.3
Triglycerides	-8.1	-19.3;3.1	-4.8	-15.3;5.7
BMI	-1.6	-3.4;0.3	-1.2	-3.0;0.5
Diabetes	-32.8*	-57.1;-8.5	-15.6	-38.7;7.6
Coronary factors				
Current smoke exposure	-20.9	-44.3;2.5	-20.5	-42.4;1.3
Self reported history of CHD	-5.8	-23.4;11.9	1.7	-15.0;18.4
Self reported history of stroke/TIA	-12.9	-37.8;12.1	-7.4	-31.2;16.5
Coronary calcification	-3.2	-6.5;0.1	-1.9	-5.0;1.3
Minor ECG abnormalities	-15.2	-33.2;2.7	-5.0	-22.0;12.0
Major ECG abnormalities	-21.7*	-41.1;-2.3	-19.1*	-37.3;-1.0

Data presented as B or 95% CI. Analysis of data using linear regression models with tCBF (mL/min) as dependent variable and late-life cardiovascular determinants as independent variable. * $p<0.05$

BP = blood pressure; BMI = body mass index; CHD = coronary heart disease; TIA = transient ischemic attack; ECG = electrocardiogram.

Model 1: adjusted for age and sex

Model 2: additional adjustment for MRI infarct and brain volume

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Discussion

We found tCBF in elderly subjects depends on several different hematologic, hemodynamic, metabolic and coronary characteristics. Moreover, based on the mid-life data, these factors begin early to affect tCBF. Strengths of this study include the large sample from a population based cohort. Furthermore, a wide range of cardiovascular factors was investigated. Combining mid-life and late-life data allowed representation of life course associations with tCBF. To determine tCBF, we used 2D phase-contrast imaging, which has been shown to be accurate and reliable.[4] Additionally, the method to analyze the imaging files was automatic and validated.[9]

There are some issues need to be taken into account when interpreting the results. We did not have tCBF measures at mid-life, so we do not have an estimate of the decline in tCBF associated with the factors we investigated. We also do not have a measure of brain volume acquired concurrently with the tCBF, so there may be some residual confounding due to brain volume. Finally, subjects with poorer health status (and expected lower tCBF) are less likely to participate, and this may underestimate the significance of the association of tCBF to the characteristics of interest.

Independent of age, sex, infarcts and brain volume, both hemotologic factors were strongly inversely associated with tCBF, such that tCBF declined with increasing levels of hemoglobin and hematocrit. The reduced flow associated with these hematologic measures has been described before, but never in such a large population based study.[1, 13-16] The changes in tCBF are thought to be the result of cerebral autoregulation, which reacts to both blood viscosity and arterial oxygen.[14, 16] It is believed that an increase in viscosity (e.g. caused by an increase of hemoglobin and hematocrit) leads to increased vascular resistance and a decrease in flow.[1, 13] Indeed, we found an inverse association of hemoglobin to tCBF in those with higher levels of hemoglobin and not in those with lower levels. However, possibly, there is a J shaped relationship of hemoglobin to tCBF that we could not detect. Active vasodilatation occurs in reaction to arterial oxygen content,[15] ensuring that, for example during anemia, CBF is increased. In this present sample, none of the subjects fulfilled criteria for anemia, and the test for non-linearity of the associations of hemoglobin to tCBF, was not significant. A larger sample size at the lower ends of hemoglobin levels may be needed to detect a non-linear association. However, the lack of association in the lower hemoglobin strata may also indicate a diminished capacity in old age for cerebral autoregulation to increase tCBF in reaction to low hemoglobin, or an increase in dehydration; this needs to be investigated in future studies. Further, earlier studies reported elevated hematocrit levels were associated carotid occlusion, and an increased risk for ischemic stroke and related mortality.[17, 18] Although carotid occlusion will have direct effects on tCBF, the reaction of tCBF to high hematocrit may play a crucial role in the development of brain ischemia. This is of interest since in ischemic stroke, high hematocrit has been associated with a reduced reperfusion and larger infarct size.[19]

We found both mid- and late-life levels of diastolic blood pressure, and late-life MAP and major ECG abnormalities were associated with tCBF. There was no relation between systolic blood pressure, pulse pressure and tCBF. These results suggest the hypothesis that peripheral resistance and cardiac output are important initial factors related to total blood flow to the brain later in life. On the other hand, diabetes was associated with tCBF when adjusting for age and sex, but not after adjusting for brain volume and infarcts. This suggests glycemic or insulin dysregulation may be associated with tCBF through its effect on brain perfusion or neurodegeneration. The relation between diabetes and tCBF has previously been investigated, but characteristics of the samples vary and results are conflicting. [20]

In summary, we found that multiple factors have to be considered when investigating tCBF in elderly; strong inverse relations of tCBF to hemoglobin, hematocrit, diastolic blood pressure, and cardiac function were shown. Future research should be aimed at further unraveling the interactions among characteristics of blood, heart and blood flow to the heart and brain, and evaluate the significance in clinical practice. In this study, mid-life characteristics showed comparable associations with tCBF in elderly, which illustrates the importance to recognize cardiovascular disease early in life.

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2.2 Longitudinal MRI measures predict total cerebral blood flow in the AGES-Reykjavik study

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Abstract

Objective

Using magnetic resonance images, we investigated the association of total cerebral blood flow (tCBF) and total brain perfusion (tBP) to vascular lesions and a change in measures of brain structure.

Methods

Baseline (T1) scans were acquired on the population based cohort of men and women (b 1907 – 1935) participating in the AGES-RS. A mean (SD) 2.3 (0.1) yrs after T1, a random, non-demented, sub sample of the cohort (n=206, age 75±5y, 55% women) was invited for a follow-up scan (T2) that included two-dimensional phase contrast imaging to determine tCBF (mL/min) and tBP; (tCBF per 100mL brain volume). Blood flow measures were examined in association with baseline presence of infarcts and microbleeds, and with annual change in brain tissue volumes estimated with automated computer algorithms. The associations were estimated with linear regression adjusted for age and sex.

Results

Mean (SD) tCBF was 577(101mL/min) and mean (SD) tBP was 53.6 (9.4) mL/min per 100mL. Presence of vascular lesions at T1 were not associated with tCBF or tBP. Decrements in volumes of whole-brain tissue were significantly associated with tCBF ([95%CI]; -40.9 [-75.7;-4.5]) and tBP (-3.2 [-6.1;-0.1]); grey matter with tCBF (-30.3 [-60.3;-0.4]) and(tBP -3.0 [-5.7;-0.4]). Annual progression of white matter hyperintensities (WMH) was significantly associated with lower tBP (-12.2 [-21.1;-3.4]).

Conclusion

The association of whole-brain and grey matter tissue loss and progression of WMH to lower tCBF and lower total brain perfusion, suggests brain tissue damage leads to a decreased demand for blood, and possibly a cycle of reduced demand and cerebral damage.

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Introduction

Increasing age is associated with decline in total cerebral blood flow (tCBF).[1-3] This decline is partly determined by brain volume, which may be associated with neurodegeneration, as well as large and small vessel disease. However, not clear is the extent to which brain tissue loss (atrophy in the gray and white matter) and evidence of cerebrovascular damage contribute to a decline in tCBF. Most likely there is a vicious circle, whereby reduced tCBF leads to ischemic changes and atrophy, and these pathologies lead to reduced demand for blood.

Grey matter has a higher demand for perfusion. However, most studies report on changes in the white matter. For example, cross-sectional studies have shown an inverse relation between the severity of white matter hyperintensities (WMH) and both tCBF and tBP (tCBF per 100mL brain volume).[3-5] These associations have been reported to be stronger in the presence of subcortical brain atrophy (lower tBP).[4] One previous study reported an inverse association of tCBF to progression of periventricular and deep WMH with a stronger relation for periventricular lesions.[6]

As far as we know, there are no longitudinal studies of the association blood flow measures and of progression of brain atrophy and vascular damage. In non-demented elderly, age-related atrophy rates ranging from 0.2% to 0.7% per year, and progression rates of WMH of 0.05% of brain volume have been reported.[7-10] Understanding the temporal association of changes in brain structure and blood flow will help to inform us on the trajectory of pathological brain aging and help identify proximal factors leading to these pathologic changes. Here we aim to study the association of vascular lesions, brain tissue volume, and progression of brain changes to tCBF and tBP. Data are based on a non-demented subsample participating in the population-based Age Gene/Environment Susceptibility – Reykjavik Study (AGES-Reykjavik).

Methods

Study population

The design of the AGES-Reykjavik has been described previously.[11] Briefly, the AGES-Reykjavik cohort is based on the Reykjavik Study, a community-based cohort established in 1967 to prospectively study cardiovascular disease in Iceland. In 2002 the study was extended to the AGES-Reykjavik Study. Between 2002 and 2006 5764 men and women participated in detailed evaluations of cardiovascular, musculoskeletal, metabolic and neurocognitive phenotypes, including MRI scanning of the brain (time point 1; T1). AGES-Reykjavik was approved by the National Bioethics Committee in Iceland, which acts as the institutional review board for the Icelandic Heart Association (approval number VSN-00-063), and by the National Institute on Aging Intramural Institutional Review Board. All participants gave written informed consent.

This study includes participants whose T1 MRI was acquired between March 2004 and January 2005 (figure 1). Between 2006 and 2007 a random sub sample of these participants who were not demented at T1 (n=408) were invited for a repeat brain MRI (time point 2; T2). The MRI protocol of half of this subgroup (n=206) was the same as in T1, but also included the MRI sequence necessary for tCBF determination. The mean (SD) time interval between T1 and T2 was 2.3 (0.1) years (see Figure 1).

MRI protocol

At T1 and T2, MRI was performed on a 1.5 Tesla machine (General Electric Medical Systems, Waukesha, Wisconsin, USA) following a standard protocol that included a PD/T2w FSE sequence (proton density/T2-weighted fast spin echo; field of view [FOV] 220 mm, matrix 256x256, slice thickness 3.0mm, echo time [TE] 22ms, TE 90ms, repetition time [TR]: 3220ms, echo train length 8, flip angle 90°), a FLAIR sequence (fluid attenuated inversion recovery; FOV 220mm, matrix 256x256, slice thickness: 3mm, TE: 100ms, TR: 8000ms, inversion time [TI] 2200ms, flip angle 90°) and a T2*-weighted gradient echo based echo planar imaging (GRE-EPI) sequence (FOV 220mm, matrix 256x256, slice thickness 3mm, TE 50ms, TR 3050ms, flip angle 20°). Additionally, images were acquired with a T1-weighted three-dimensional spoiled gradient echo sequence (FOV 240mm, matrix 256x256, slice thickness 1.5mm, TE 8ms, TR 21ms,

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flip angle 30°). All images were acquired to give full brain coverage. Slices were angled parallel to the anterior commissure-posterior commissure line to give reproducible image views in the oblique-axial plane.

Two-dimensional (2D) phase contrast MR angiography is a non-invasive and fast method to measure tCBF and has been shown to be accurate and reliable.12 At T2 the 2D phase contrast sequence was added as follows. First, a sagittal 2D phase contrast MRI angiographic scout image was acquired (FOV 220mm, matrix 256x256, TE 6.1ms, TR 33ms, flip angle 30°, velocity encoding 80cm/sec, slice thickness 60mm). On this scout image, an oblique transverse imaging plane perpendicular to the carotid arteries and the basilar artery was chosen for a 2D gradient-echo phase contrast sequence (FOV 220mm, matrix 256x256, TE 6.2ms, TR 20ms, flip angle 9°, velocity encoding 100cm/sec, slice thickness 5mm).

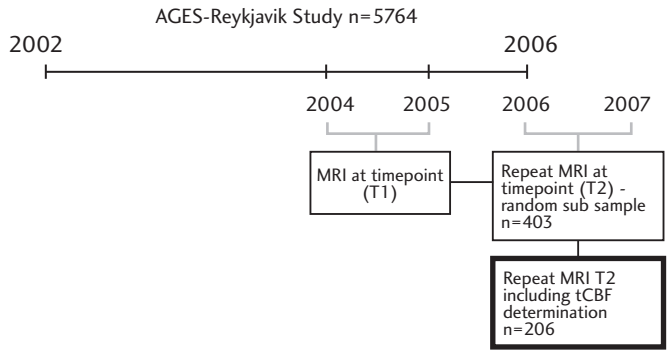

Figure 1; Study design

Between 2002 and 2006 n=5764 subjects participated in the baseline examination of the AGES-Reykjavik study. We included participants whose MRI was acquired between March 2004 and January 2005 (= time point 1; T1). Between 2006 and 2007 a random sub sample these participants (n=408) were re-invited for repeat brain MRI (time point 2; T2). The MRI protocol of half of this subgroup (n=206) included a MRI sequence necessary for tCBF determination.

Measurement of total cerebral blood flow

The images of the cerebral blood flow were analyzed using the software package FLOW (Division of Image Processing, Department of Radiology, Leiden University Medical Center).13 This software provides automated detection of the vessel lumen boundaries and subsequent quantification of flow and velocities. The only user-interaction required is the manual placement of a seed point in each of the vessels to be analyzed. All determinations were performed by the same person, with an excellent agreement between repeated blood flow measurements of 20 scans (coefficient of variation 1.7%). The resultant value of the mean signal intensity in each vessel represented the spatial- and time averaged flow velocity in that vessel, which was expressed in cm/sec. By multiplying this average velocity by the cross-sectional area of the pixels in the vessel, the flow rate (in mL/s) of the carotid arteries and the basilar artery are calculated. Subsequently, the flow rates of the carotid arteries and the basilar artery are summed and multiplied by 60sec/min to calculate tCBF (mL/min). As representation of stationary tissue, ideally the velocity measured in background tissue should be zero. However, the flow sequences had some offset velocity (likely inherent to the scanner and used methodology). Therefore, a fourth region of interest (ROI) was drawn in the pons, and the average velocity in this fourth ROI was subtracted to correct for the velocity offset (median [min-max] 1.0 [0.2-1.5] cm/sec).

Brain volumes

For T1 and T2 MRIs, volumes of grey and white matter, WMH and cerebrospinal fluid (CSF) were computed automatically with an algorithm based on the Montreal Neurological Institute (MNI) pipeline.[14]

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The AGES-Reykjavik/MNI pipeline has been modified to accommodate full brain coverage including cerebellum and brain stem, multi-spectral analysis using T1-weighted 3D SPGR, FLAIR and PD/T2-weighted FSE images, high throughput, automatic skull removal and minimal editing. Total brain volume was determined by summing the volumes of the grey matter, white matter and WMH. Intracranial volume (ICV) was obtained by adding the volumes of CSF to the total brain volume. To correct for inter-individual differences in ICV, total brain fraction, was calculated by dividing the brain volume by ICV and expressed as percentage. Similarly, grey matter, white matter and WMH fraction were calculated.

Infarct-like lesions and microbleeds

On MRI at T1, cerebral infarct-like lesions were defined as parenchymal defects, areas isointense to cerebral spinal fluid on all pulse sequences with a minimum diameter of 4mm, except for cerebellar infarcts, which had no size criteria. No clinical data was reviewed for these infarct-lesions found on MRI; however, for easier reading we; hereafter call these lesions infarcts. The infarcts were classified as cortical, subcortical or cerebellar infarcts. Cortical and cerebellar infarcts were identified by a neuro-radiologist and radiographically described by three trained radiographers who also identified and described subcortical infarcts. Five percent of all scans were re-read without knowledge of the prior reading, at the Department of Radiology, LUMC, the Netherlands, to assess inter-rater reliability (weighted kappa = 0.7). Average intra-rater reliability based on repeated ratings of 19 cases once every year by each observer over the course of the study was 0.9.

As previously described,15 microbleeds were defined as a focal area of signal void within the brain parenchyma that: (1) is visible on T2*-weighted GRE-EPI images and is smaller or invisible on T2-weighted FSE images; (2) is not abutting a parenchymal defect; and (3) does not show any other structure in the aria of signal void. Areas of symmetric hypointensities of the globus pallidus likely to represent calcification or non-hemorrhagic iron deposits were excluded. The presence of microbleeds was assessed

Covariates

At T1, subjects were administered a questionnaire about medical history; presented currently used medication vials; underwent a clinical examination including blood pressure measures and had a fasting blood sample drawn. To control for factors that may modulate blood flow to the brain we controlled for major cardiovascular risk factors. Hypertension was defined as a self reported doctor's diagnosis of hypertension, the use of blood pressure lowering drugs, or a systolic blood pressure ≥140mmHg or a diastolic blood pressure of ≥90mmHg. We considered diabetes present if a history of diabetes was reported, if a subject was taking oral hypoglycemic medication or insulin, or if fasting plasma glucose was ≥7.0mmol/l (≥126mg/dl). Smoking status was assessed by self report and defined as never, former or current smoker.

Data analysis

Definition of analytical variables.

Per subject, tBP(in mL/min per 100mL) was calculated by dividing total cerebral blood flow (mL/min) by brain volume (mL) and multiplying the result by 100. Infarcts and microbleeds were coded as present or absent. Brain tissue volumes were normally distributed with the exception of WMH; which was transformed with the natural log plus 1 (ln [1+WMH fraction]). To investigate whether the brain volume measures significantly changed in the 2 year interval we compared brain tissue measures atT1 and T2 with paired sample t-tests, and for WMH fraction using the Wilcoxon rank test for non-parametric data. Annual change in tissue volume was calculated as the difference in tissue fractions between T1 and T2, divided by the time interval in years between the assessments. Annualized measures were expressed as change in percent of TICV per year.

We used linear regression models to assess the relation of blood flow measures to tissue volume (cross-sectional at T2), presence of vascular lesions measured at T1, and annual change from T1 to T2. All regression analyses were adjusted for age and sex (model 1), and additionally adjusted for hypertension, diabetes and smoking status (model 2). Statistical analyses were performed using SPSS 14.0 for Windows (SPSS Inc). Statistical significance was set at $p<0.05$.

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Results

At T2, the sample had a mean±SD age of 78±5 years and 55% were women (table 1). Mean total brain volume was 1083±99mL with a total brain fraction of 71.5% Mean tCBF was 577±101mL/min, and mean tBP was 53.6±9.4mL/min per 100mL brain volume.

Cross-sectional associations

We found no relation of age to tCBF (per SD increase of age, difference in tCBF -2.0 [95%CI = -4.7;0.6]) or tBP 0 [95%CI = -0.2;0.3). Men and women had comparable tCBF and comparable flow values in both carotid arteries and the basilar artery (tCBF M: 569±109mL/min, F: 584±95mL/min; left carotid artery M: 227±61mL/min, F:233±55 mL/min; right carotid artery M: 226±54 mL/min, F: 229±52 mL/min; basilar artery M:115±39 mL/min, F: 122±37 mL/min). tBF was higher in women (mean 56.3±8.9mL/min per 100mL) compared to men (mean 50.3±8.9mL/min per 100mL; independent sample t-test p<0.001). Cross-sectionally, tCBF was positively associated with total brain fraction (per SD increase of brain fraction, difference in tCBF 8.0 [95%CI = 3.8; 12.2]) (table 2). This was attributable to significant associations of tCBF to both grey matter and white matter. Grey matter volume was positively associated with tBP. WMH were significantly associated with tBP in model 1, but this was attenuated in model 2.

Longitudinal associations

At T1, the prevalence of infarcts was 31% and microbleeds were found in 13% of the subjects. Adjusting for age and sex, neither infarcts (any, or any infarcts in thesubcortical, cortical or cerebellar regions) or microbleeds, were associated with tCBF (p value for all >0.16) or with tBP (p values for all >0.16) (table 3). Additional adjustment for hypertension, diabetes and smoking status did not change these results (table 4).

Total brain volume and total brain fraction decreased (respectively from 1099mL to 1083mL; 72.6% to 71.5%) from T1 to T2, with a mean annual loss of 0.5±0.4% per year of total intracranial volume. The mean annual loss of grey matter was 0.4±0.5% , and of WM was 0.2%. Total WMH volume increased from a median (interquartile range) volume of 12mL (7-23) to 15mL (7-28) with an annual progression of WMH of 0.06% (0.02-0.13). Adjusting for age and sex, all brain volume measures changed significantly (p <0.001) over the 2.3 year interval.

There was a trend between higher annual whole-brain atrophy and lower tCBF, which was strengthened after adding to the model smoking status, hypertension and diabetes (table 4). This association mainly reflected the changes in the grey matter. Furthermore, there was a significant decrease in tBP as WMH increased and grey matter decreased.

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Table 1; Characteristics of participants: AGES-Reykjavik Study

Number of participants	206
Sex n (% women)	114 (55%)
Age –T1 (y)	75 (5)
Hypertension	163 (79%)
Diabetes	21 (10%)
Former smoker	93 (45%)
Current smoker	22 (11%)
MRI image interval T1-T2 (y)	2.3 (0.1)
MRI T1	
Any Infarct present (%)	64 (31%)
Cortical infarct present (%)	21 (10%)
Subcortical infarct present (%)	14 (7%)
Cerebellar infarct present (%)	45 (22%)
Microbleeds ≥1 present (%)	26 (13%)
MRI T2	
Total cerebral blood flow (mL/min)	577 (101)
Total brain perfusion (mL/min per 100mL)	53.6 (9.4)

Data presented as number (%) or mean (SD)

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Table 2; Cross-sectional association of brain tissue, tCBF and tBP: AGES-Reykjavik Study

	Model	Total cerebral blood flow (mL/min)		Total brain perfusion (mL/min per 100mL)	
		B	95%CI	B	95% CI
Grey matter fraction	1.	7.3	2.4;12.2	0.6	0.1;1.0
	2.	6.4	1.5;11.3	0.5	0.1;1.0
White matter fraction	1.	13.0	5.4;20.5	0.3	-0.4;1.0
	2.	9.2	1.3;17.1	0.0	-0.7;0.7
WMH fraction	1.	-25.7	-57.9;6.6	-3.4	-6.3;-0.6
	2.	-13.6	-45.8;18.6	-2.5	-5.4;0.3
Total brain fraction	1.	8. 0	3.8;12.2	0.3	-0.04;0.7
	2.	6.7	2.5;10.9	0.2	-0.1;0.6

Data presented as adjusted mean differences (95% confidence interval) in total cerebral blood flow or total brain perfusion per unit increase in total brain fraction, grey matter fraction, white matter fraction or WMH fraction. Please note that for WMH fraction statistical analysis was performed using log-transformed values.
WMH = white matter hyperintensity
Model 1: adjusted for age and sex
Model 2: adjusted for age, sex, hypertension, diabetes, smoking status

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Table 3; Infarcts and microbleeds in relation to tCBF and tBP: AGES-Reykjavik Study

	Model	Total cerebral blood flow (mL/min)		Total brain perfusion (mL/min per 100mL)	
		B	95%CI	B	95% CI
Any infarct	1.	-19.0	-49.8;11.7	-1.3	-4.1;1.5
	2.	-10.8	-41.1;19.5	-0.6	-0.2;0.3
Cortical infarct	1.	-38.0	-94.1;18.0	-3.5	-8.5;1.4
	2.	-27.6	-83.0;27.7	-2.9	-7.8;2.1
Subcortical infarct	1.	-21.5	-67.6;24.7	-2.2	-6.3;1.9
	2.	-4.3	-50.4;41.7	-1.0	-5.1;3.2
Cerebellar infarct	1.	-24.4	-58.4;9.6	-1.6	-4.7;1.5
	2.	-19.3	-52.6;13.9	-1.1	-4.2;1.9
Microbleeds	1.	-10.6	-53.1;31.8	-1.9	-5.7;2.0
	2.	-10.0	-51.6;31.6	-1.7	-5.5;2.1

Data presented as adjusted mean differences (95% confidence interval) in total cerebral blood flow or total brain perfusion for presence of any infarct, a cortical infarct, a subcortical infarct, a cerebellar infarct or ≥1 microbleed.
Model 1: adjusted for age and sex
Model 2: adjusted for age, sex, hypertension, diabetes, smoking status

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Table 4; Association of annualized change in brain tissue, tCBF and tBP: AGES-Reykjavik Study

		Total cerebral blood flow (mL/min)		Total brain perfusion (mL/min per 100mL)	
		B	95%CI	B	95% CI
Annual grey matter atrophy	1.	-22.9	-53.7; 7.9	-2.6	-5.3;0.2
	2.	-30.4	-60.3;-0.4	-3.0	-5.7;-0.4
Annual white matter atrophy	1.	-39.1	-100.4;22.1	-2.3	-7.7;3.1
	2.	-25.9	-85.9;34.1	-1.4	-6.7;4.0
Annual WMH progression	1.	-97.2	-200.2;5.8	-12.2	-21.2;-3.2
	2.	-96.2	-196.4;3.9	-12.2	-21.1;-3.4
Annual whole-brain atrophy	1.	-34.6	-71.3;2.1	-2.9	-6.2;0.3
	2.	-40.9	-75.7;-4.5	-3.2	-6.4;-0.1

Data presented as adjusted mean differences (95% confidence interval) in total cerebral blood flow or total brain perfusion for unit annualized change of brain tissue.
WMH = white matter hyperintensity
Model 1: adjusted for age and sex
Model 2: adjusted for age, sex, hypertension, diabetes and smoking status

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Discussion

Cross-sectionally, adjusting for age and sex, tCBF was associated with total brain tissue, specifically grey and white matter volumes. tBP was most strongly positively associated with grey matter volume. We report an association of an annual decrease in grey matter, whole-brain tissue volume and lower tCBF. Annual progression of WMH and grey matter loss were significantly associated with tBP.

Strengths of the current study include the use of an accurate and reliable measure of tCBF with 2D phase-contrast imaging.[12] Contrary to most other techniques, it is a non-invasive method which allowed us to determine tCBF in a relatively large sample. The study was population based, including only non-demented elderly. Furthermore, we used a validated and automatic method to estimate tissue volume from the scans. Finally, all analyses with brain tissues were corrected for intracranial volume. One limitation of the study is the absence of baseline tCBF values, which would give insight into the magnitude of decline in cerebral blood flow and perfusion that follows a change in brain tissue volume. Further, although all of the coefficients suggested decline in tCBF with decreasing brain tissue, the sample may be too small to find significant differences.
Values for mean tCBF were comparable to some earlier studies in older samples,[16,17] but slightly higher compared to others.[1,3] Recently reported values for total brain perfusion measured with 2D phase-contrast imaging were a little lower (respectively 51.2 and 52.2 mL/min per 100mL) compared to the mean total brain perfusion we found of 53.6mL/min per 100mL brain volume, likely reflecting differences in research population and assessment methodologies.[3,4] In this study, delineation of the vessel was automatic, while the previous reports used a manual method. Furthermore, we corrected for background offset that might have influenced our results.

Consistent with other cross-sectional studies,[3] decreasing brain volumes, including total brain volume, grey and white matter volumes, were related to decreasing tCBF. Annual grey matter and whole-brain tissue volume loss were significantly associated with lower tCBF after correction for vascular risk factors. This likely reflects the normally higher perfusion in grey compared to white matter[18]; possibly more atrophy is needed to detect a significant effect.[19] As far as we know, no previous study examined the association of annualized change of brain tissue to tCBF.
Our results suggest reduced demand from the atrophying brain leads to lower blood flow to the brain. A third time point is needed to determine whether lower blood flow and perfusion leads to more atrophy and WMH.

We found cross-sectionally and longitudinally, WMH reduces brain perfusion, but not tCBF, consistent with other.[19,20] In the one study that examined the association between progression of WMH and tCBF, a stronger association was found with lesions located in the periventricular compared to deep white matter. Interestingly, we did not find a relation between presence of infarcts or microbleeds and tCBF or tBP at follow up. By definition brain perfusion is decreased in acute ischemic stroke, but the longitudinal effects of infarcts and microbleeds on tCBF and total brain perfusion have to be further elucidated in future research.
Together, our findings concerning WMH and atrophy suggest that tissue damage results in a lower demand of blood flow and lower total brain perfusion, but we cannot exclude that this was preceded by lower tCBF in the first place. Future research is needed to confirm our hypothesis, possibly leading eventually to more emphasis on therapeutic strategies directed at the origin of WMH and atrophy instead of tCBF. With this study we feel to be one step further in understanding the complex equilibrium of total blood flow to the brain, in terms of supply and demand.

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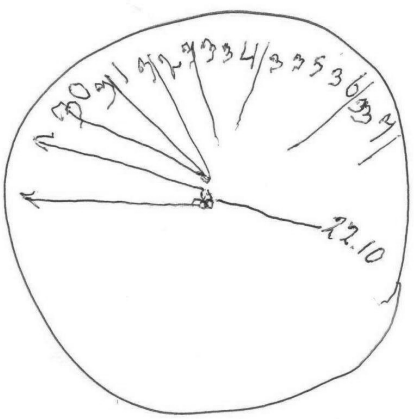
Part 3

Vascular MRI measures in mild cognitive impairment and dementia



Example of the neuropsychological clock drawing test of a patient with vascular dementia. The patient was asked to draw a clockface, with the hands indicating ten past ten.

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3.1 Progression of MCI to dementia: The contribution of cerebrovascular disease compared to medial temporal lobe atrophy

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Abstract

Objective

We sought to determine the predictive value of MRI measures of vascular disease (white matter hyperintensities [WMH], lacunes, microbleeds, infarcts) compared to atrophy on progression of mild cognitive impairment (MCI) to dementia.

Methods

We included 152 consecutive patients with MCI. Baseline MRI was used to determine the presence of medial temporal lobe atrophy (MTA) and vascular disease (prescence of lacunes, microbleeds and infarcts was determined, WMH were rated using a semiquantitative scale). Patients were followed up for 2±1 years.

Results

72 (47%) Patients progressed to dementia during follow-up. Of these, 56 (37%) patients were diagnosed with Alzheimer's disease (AD), and 16 (10%) patients were diagnosed with another type of dementia (including vascular dementia, frontotemporal lobar degeneration and Parkinson dementia). Converters were older, and had a lower mini-mental state examination (MMSE) score at baseline. On baseline MRI, patients who progressed to a non-Alzheimer dementia showed more severe WMH and had a higher prevalence of lacunes in the basal ganglia and microbleeds compared to non-converters. Cox proportional hazard models showed that adjusted for age and sex , baseline MTA (HR [95%CI] = 2.9 [1.7-5.3]), but not vascular disease, was associated with progression to AD. By contrast, deep WMH (HR 5.7 [1.2-26.7]) and periventricular hyperintensities (HR 6.5 [1.4-29.8]) predicted progression to non-Alzheimer dementia. Furthermore, microbleeds (HR 2.6 [0.9-7.5]) yielded a more than twofold increased, though non-significant risk of non-Alzheimer dementia.

Conclusion

MTA and markers of cerebrovascular disease predict the development of different types of dementia in MCI patients.

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Introduction

Mild cognitive impairment (MCI) is characterized by mild cognitive deficits not sufficient for a diagnosis of dementia.[1] MCI patients have an increased risk of progression to dementia, mostly Alzheimer's disease (AD) – although the risk of another type of dementia is known to be elevated as well.[1-3] Atrophy of the medial temporal lobe (MTA), including the hippocampus and entorhinal cortex, is a sensitive marker for AD. Visual assessment of MTA has been shown to be a powerful and independent predictor of progression to dementia in MCI patients.[4-6] Additionally, global cortical atrophy has been demonstrated to be related to progression of MCI to dementia.[7] In contrast to atrophy, the impact of cerebrovascular disease on progression to dementia is less clear.

Only a small number of longitudinal studies have examined the role of vascular disease in MCI patients, and results have been conflicting.[7-11] One study found white matter hyperintensities (WMH) to be associated with the risk of progression from normal cognitive function to MCI, but not from MCI to dementia.[7] This is in line with another report that did not find an association between cerebrovascular disease (i.e. clinical stroke, extent of WMH or presence of lacunes) and progression of MCI to dementia.[9] In contrast, others did find a relation between WMH and progression to AD in MCI patients.[10] Nonetheless, this study was small (n=27) and used computed tomography instead of magnetic resonance imaging (MRI). More recently, a study in a large sample of MCI patients, reported an association between WMH and cognitive decline.[8] Furthermore, the same group reported WMH to be related to an increased risk of vascular or mixed dementia, but not of AD.[11] Expression of vascular disease other than WMH, such as lacunes and microbleeds, was not taken into account. Little is known about the role of microbleeds and cognitive function in MCI or dementia patients, apart from one report that found a relation between microbleeds and cognitive impairment in subcortical vascular dementia.[12] Another study in non-demented patients with cerebrovascular disease reported a relation between microbleeds and executive dysfunction.[13]

The aim of this study was to assess the predictive value of MRI measures of both atrophy and vascular disease, including infarcts, WMH, lacunes and microbleeds, with respect to progression of MCI to dementia.

Methods

Patients

We consecutively recruited 152 patients with MCI from the outpatient memory clinic of the Alzheimer Centre of the VU University Medical Centre (VUmc). Standardized assessment included medical history, neurologic examination, laboratory tests, neuropsychological testing including Mini-Mental State Examination (MMSE),[14] electroencephalogram (EEG) and (MRI of the brain. Diagnoses were made in a multidisciplinary consensus meeting according to the Petersen criteria.[1] The study was approved by the local Medical Ethical Committee. All patients gave written informed consent for their clinical data to be used for research purposes.

Clinical follow-up

All patients were annually re-examined for possible alteration in cognitive function with a mean follow-up of 2 ± 1 years. Standardized assessment included careful history and cognitive testing. All patients in this study were re-evaluated at least once (maximum 5). Patients with stable or improved cognitive function at follow-up were regarded as non-converters. Patients who progressed to dementia were regarded as converters. Converters were classified in two clusters. One cluster included patients who progressed to AD. The other cluster consisted of patients who progressed to a non-Alzheimer dementia including vascular dementia (VaD), frontotemporal lobar degeneration (FTLD) and dementia with Lewy Bodies (DLB). To diagnose AD we used the criteria of the National Institute on Neurological and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA),[15] VaD was diagnosed by use of the criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale

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pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN),[16] FTLD was diagnosed by the Neary and Snowden criteria[17] and DLB was diagnosed by the Mc Keith criteria.[18]

MRI protocol

At baseline, MRI was performed on a 1.0 Tesla machine (Magnetom Impact Expert Siemens AG, Erlangen, Germany) following a standard protocol, including coronal T1-weighted 3D MPRAGE (magnetization prepared rapid acquisition gradient echo; 168 slices, field of view [FOV] 250mm, matrix 256x256, slice thickness 1.5 mm, echo time [TE]: 7ms, repetition time [TR]: 15 ms, inversion time [TI] 300 ms, flip angle 15 degrees), axial FLAIR (fluid attenuated inversion recovery, 17 slices, FOV 250mm, matrix 256x256, slice thickness: 5mm, interslice gap: 1.5mm, TE: 105ms, TR: 9000ms, TI 2200 ms, flip angle 180 degrees) and axial T2*-weighted gradient echo sequences (19 slices, FOV 250 mm, matrix 256 x 256, slice thickness 5 mm, interslice gap 1.5 mm, TE 22 milliseconds, TR 800 milliseconds, flip angle 20°).

Image assessment

Baseline MRI was used to determine presence of atrophy and vascular disease. Visual rating of MTA was performed on coronal T1-weighted images according to the 5-point (0-4) Scheltens scale, using the average score of the left and right side.[19] Global cortical atrophy (GCA) was assessed visually on axial FLAIR images (possible range of scores 0-3).[20] The degree of WMH severity was rated on axial FLAIR images using a semiquantitative scale.[21] Periventricular and deep white-matter hyperintensities were rated separately, the rating for each score being based on both size and number of lesions in different anatomical regions. Periventricular hyperintensities (PVH) were defined as lesions adjacent to the lateral ventricles or the occipital or frontal horns resulting in a score ranging from 0 to 6. Deep white-matter hyperintensities (DWMH) were defined as lesions located in the frontal, parietal, occipital, and temporal deep white matter with a maximum score of 6 for each region to give a total score ranging from 0 to 24. A total WMH score was composed by summing the PVH and the DWMH scores, ranging from 0 to 30. Ratings of basal ganglia and infratentorial hyperintensities were not included in the present study. Lacunes were defined as T1-hypointense and T2-hyperintense CSF-like lesions surrounded by white matter or subcortical grey matter with a minimum diameter of 3mm, not located in areas with a high prevalence of widened perivascular spaces (vertex, anterior commisure). Next to an overall count of lacunes, the presence of ≥1 lacune in the basal ganglia was determined. Microbleeds were defined as strongly hypointense, mostly round lesions on the axial FLASH 2D images with a diameter between 2 and 10mm. Symmetric hypointensities in the globi pallidi, most likely to be calcification or iron deposition, and flow voids artifacts of the pial blood vessels were disregarded. The presence of infarcts was determined using the different MRI sequences.

Statistical analysis

Statistical analysis was performed by means of SPSS 14.0 (SPSS Inc). For analysing purposes MRI measures were dichotomised, using for the WMH measurements the median score of the total population. This resulted in the following: severe MTA: <1.5 absent, ≥ 1.5 present; severe PVH: <3 absent, score ≥ 3 present; severe DWMH: <4 absent, ≥ 4 present; severe WMH: <6 absent, ≥ 6 present; presence of ≥ 1 lacune, presence of ≥ 1 microbleed, presence of ≥1 infarct. Group comparisons were performed using chi-squared tests for dichotomous variables and independent samples t-tests for continuous data. Next, Cox proportional hazards models, that account for varying follow-up times, were used to investigate the risk of progression to dementia depending on the various dichotomized MRI measures. The analysis was performed twice, first using progression to AD as outcome measure with the non-converters as reference group. Subsequently, progression to a non-Alzheimer dementia was analysed as second outcome measure, using again the non-converters as reference group. Data are presented as hazard ratio (HR) and accompanying 95% confidence interval (95% CI). The first model shows the crude risk estimates. In the second model we adjusted for age and sex. Significance was set at $p<0.05$.

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Results

Of the total of 152 MCI patients, 72 (47%) patients progressed to dementia during follow-up. Fifty-six patients (37%) were diagnosed with AD, and sixteen patients (10%) were diagnosed with a non-Alzheimer dementia (VaD n=7, FTLD n=5, DLB n=2, Parkinson dementia n=1, alcohol dementia n=1). Converters had a slightly longer follow-up duration and were older, more likely to be female and had a lower MMSE at baseline (table 1).

Baseline MRI measures are presented in table 2. Both patients who progressed to AD and patients who progressed to a non-Alzheimer dementia showed more MTA and more cortical atrophy than non-converters. Measures of vascular disease were more prevalent among patients who progressed to non-Alzheimer dementia compared to non-converters: the severity of WMH (both PVH and DWMH) was higher in patients who progressed to another type of dementia compared to non-converters. In addition, these patients more often had lacunes in the basal ganglia and microbleeds.

Cox proportional hazard models showed that, adjusted for age and sex, baseline MTA predicted progression to AD (HR 2.9 [1.7-5.3]) (table 3). None of the measures of vascular disease predicted progression to AD. A different picture emerged looking at progression to non-Alzheimer dementia. Adjusted for age and sex, severe WMH (HR 5.8 [1.2-26.6]) was strongly associated with progression to non-Alzheimer dementia. This association was attributable to both PVH (HR 6.5 [1.4-29.8]; example see figure 1) and DWMH (HR 5.7 [1.2-26.7]), with the highest risk for PVH. Furthermore, the presence of microbleeds inferred almost threefold, though non-significant, increased risk of progression to non-Alzheimer dementia (HR 2.6 [0.9-7.5]). The same was seen for the presence of lacunes in the basal ganglia, which showed a more than twofold, though non-significant, predictive value on progression to non-Alzheimer dementia (HR 2.4 [0.8-7.5]. These results remained essentially unchanged after additional adjustment for MTA or MMSE (data not shown). Moreover, MTA showed a twofold, though non-significant increased risk for progression to non-Alzheimer dementia (HR 2.5 [0.8-7.2]; example see figure 2).

Table 1; Baseline characteristics

	Non-converters	Converters	AD	Non-Alzheimer dementia
Number of patients n(%)	80 (53%)	72 (47%)	56 (37%)	16 (10%)
Follow-up duration	1.8 (1.1)	2.2 (1.3)*	2.2 (1.3)	2.2 (1.4)
Age (years)	68 (9)	72 (7)**	72 (7)*	75 (6)**
Sex , women n(%)	31 (39%)	40 (56%)*	33 (59%)*	7 (44%)
MMSE – baseline	27 (2)	26 (2)**	26 (2)**	27 (2)
MMSE – follow up#	27 (2)	20 (5)***	20 (5)***	21 (5)**

Data presented as mean(SD) or n(%)
Comparison of data using chi-square or t-test when appropriate using the non-converters as reference group.
available of n=113. Compared to non-converters: * p<0.05; ** p<0.01; *** p<0.001

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Table 2; Baseline MRI characteristics

	Non-converters	Converters	AD	Non-Alzheimer dementia
MTA	0.7 (0.8)	1.4 (0.9)***	1.4 (1.0)***	1.2 (0.8)**
Cortical atrophy	0.6 (0.7)	1.0 (0.8) **	1.0 (0.7)**	1.2 (0.9)**
PVH	2.3 (1.7)	2.9 (1.6)	2.6 (1.5)	3.8 (1.5)**
DWMH	4.9 (5.4)	5.4 (5.2)	4.4 (4.6)	8.9 (5.6)**
Total WMH	7.1 (6.9)	8.3 (6.5)	6.9 (5.9)	12.7 (6.9)**
Presence ≥1 lacune n(%)	15 (19%)	15 (21%)	10 (18%)	5 (31%)
Presence of ≥1 lacune BG n(%)	9 (11%)	13 (18%)	8 (14%)	5 (31%)*
Presence of ≥1 MB n(%) #	11 (15%)	10 (16%)	4 (9%)	6 (38%)*
Presence of ≥1 infarct n(%)	5 (6%)	4 (6%)	3 (5%)	1 (6%)

Data presented as mean(SD) unless otherwise specified
Comparison of data using chi-square or t-test when appropriate using the non-converters as reference group. # missing non-converters n=5, AD n=9
Compared to non-converters: * p<0.05; ** p<0.01; ** p<0.001. Abbreviations: AD Alzheimer's disease, MTA medial temporal lobe atrophy, PVH periventricular hyperintensities, DWMH deep white matter hyperintensities, total WMH total white matter hyperintensities (sum of PVH and DWMH), BG basal ganglia, MB microbleed

Table 3; Cox regression analysis

	AD		Non-Alzheimer dementia	
	Model 1	Model 2	Model 1	Model 2
MTA	2.9 (1.7-5.0)	2.9 (1.7-5.3)	2.9 (1.1-7.9)	2.5 (0.8-7.2)
GCA	1.6 (0.8-3.1)	1.4 (0.7-2.7)	2.4 (0.8-7.0)	2.2 (0.7-7.0)
PVH	1.3 (0.7-2.2)	1.1 (0.7-2.0)	7.3 (1.7-32.4)	6.5 (1.4-29.8)
DWMH	1.4 (0.8-2.4)	1.3 (0.8-2.3)	5.7 (1.3-25.5)	5.7 (1.2-26.7)
Total WMH	1.3 (0.8-2.2)	1.2 (0.7-2.2)	6.0 (1.3-26.8)	5.8 (1.2-26.6)
Lacunes	1.2 (0.6-2.4)	1.1 (0.5-2.2)	2.3 (0.8-6.8)	2.1 (0.7-6.4)
Lacunes basal ganglia	1.4 (0.7-3.0)	1.2 (0.6-2.6)	2.7 (0.9-8.1)	2.4 (0.8-7.5)
Microbleeds	0.7 (0.3-2.0)	0.8 (0.2-2.2)	2.5 (0.9-7.2)	2.6 (0.9-7.5)
Infarcts	0.8 (0.3-2.6)	1.1 (0.3-3.8)	0.8 (0.1-6.6)	1.4 (0.2-12.1)

Data presented as HR(95% CI). Cox regression analysis comparing progression to 'AD' and 'non-Alzheimer dementia' with non-converters. The first model unadjusted, second model adjusted for age and sex.
Abbreviations: AD Alzheimer disease, MMSE mini mental state examination, MTA medial temporal lobe atrophy, GCA global cortical atrophy, PVH periventricular hyperintensities, DWMH deep white matter hyperintensities, total WMH total white matter hyperintensities (sum of PVH and DWMH)

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Discussion

We showed that in MCI patients, MTA and markers of cerebrovascular disease predicted progression to different types of dementia. MTA was a risk factor for progression from MCI to AD, while conversely the presence of cerebrovascular disease was independently associated with progression of MCI to a non-Alzheimer dementia, mostly VaD.

The role of atrophy in progression to dementia has been shown before. Earlier reports already noted visual assessment of MTA as good predictor of progression of MCI to dementia.[4-6] MTA has been shown to be present not only in patients with AD but also in other dementias (like VaD and DLB).[22-24] This is in line with our, although nonsignificant, more than twofold increased risk of MTA for progression to a non-Alzheimer dementia.

There has been a growing interest lately in the possible influence of vascular factors in the development of AD. Vascular risk factors, like hypertension and diabetes, have been associated with an elevated risk of AD, and AD patients have been reported to show more vascular abnormalities on MRI than controls.[25-29] Contrary to our expectation, we did not find any relation between presence of cerebrovascular disease on baseline MRI and progression to AD. With respect to WMH, this is in line with some[9, 11] but not all[10] previous reports. However, the latter study was small and used CT instead of MRI.10 Although we found no influence of WMH on progression from MCI to AD, progression to non-Alzheimer dementia was strongly associated with both PVH and DWMH, with the highest risk attributable to PVH. These findings confirm the recently reported predictive value of DWMH and especially PVH for vascular or mixed dementia.[11] Others did not find a predictive value of WMH for progression to non-Alzheimer dementia.[7],[9] Nonetheless, in both last mentioned studies the number of patients was small (respectively 3 patients and 7 patients). We had a sample of 16 patients who progressed to a non-Alzheimer dementia. Of these, the largest subgroup consisted of VaD. Still, the effect did not seem attributable to this group alone, since especially in patients with Parkinson dementia, DLB and alcohol dementia, we observed vascular disease as well. We are not sure how to interpret this finding. It is known that cerebrovascular disease can cause parkinsonism.[30] Alternatively, it must be noted that diagnosis was based on clinical criteria, leaving the possibility of mixed disease. Unfortunately, the sample size did not allow examination of progression to specific dementia types other than AD.

We demonstrated that the prevalence of lacunes in the basal ganglia was higher in patients who progressed to non-Alzheimer dementia compared to non-converters. A population based study showed that silent, mostly lacunar brain infarcts were a risk factor for dementia.[29] Other reports in MCI patients did not find an association between lacunes and progression to dementia.[9, 31] In this study, Cox analysis of lacunes in the basal ganglia was, although borderline significant; suggestive of a more than twofold elevated risk of progression to a non-Alzheimer dementia. We did not find a predictive value of large vessel infarcts on progression of MCI to dementia. Although having a (large vessel) stroke is known to double the risk of dementia,[32] in MCI patients the absence of progression related to infarcts has been reported before.[9] A study in patients with VaD found that patients with multi-infarct or strategic infarct dementia were predominantly diagnosed directly from a cognitive normal status, whereas patients with VaD based on small vessel disease often go through a stage of MCI.[33]

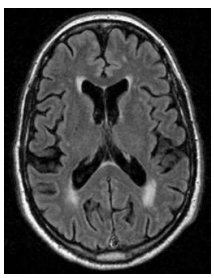

Figure 1;
Axial FLAIR image of a patient diagnosed after one year of follow-up with DLB, showing beginning confluent WMH mainly around the ventral and occipital horns of the lateral ventricles. Additionally this patient showed a lacune in the nucleus caudatus and two microbleeds (images not shown).

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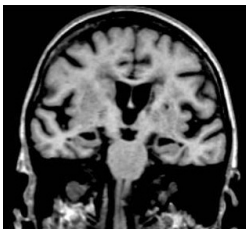

Figure 2;
Coronal T1-weighted image of a patient diagnosed after two years of follow up with vascular dementia, showing a MTA score 2 on the left and the right side. In addition, this patient showed confluent WMH, two lacunes (paraventricular and basal ganglia left hemisphere) and one microbleed (images not shown)

Our study showed that the prevalence of microbleeds was higher in patients who progressed to a non-Alzheimer dementia compared to non-converters. Furthermore, the presence of microbleeds showed an almost threefold, borderline significant risk for progression to a non-Alzheimer dementia. Little research has been performed on the role of microbleeds in MCI patients, and on microbleeds in relation to cognitive dysfunction. A study in 86 patients with subcortical VaD found microbleeds to be related to all cognitive domains with the exception of language function.[12] Another study in non-demented patients with cerebrovascular disease found a relation between microbleeds and executive dysfunction.[13] Microbleeds are presumed to reflect cerebral amyloid angiopathy (CAA), a type of cerebrovascular pathology found with an incidence of 80-98% in AD.[34, 35] In the current study, we did not find a higher prevalence of microbleeds and patients who progressed to AD compared to non-converters. Nonetheless, our results suggest that microbleeds are a risk factor for progression to a non-Alzheimer dementia.

Among the limitations of this study is the use of visual rating scales of MRI markers. Volumetric measures of MTA and WMH could lead to different effect sizes, at the cost of being less generalizable to clinical practice. A complex issue is the role of MRI in the follow-up diagnosis, even though the diagnosis of dementia basically is a clinical diagnosis. At baseline none of the patients fulfilled the clinical criteria of dementia and progression to dementia itself will not have been influenced by the MRI scan. In assessing the specific dementia types, MRI may have been used as a supportive element and therefore may have induced some circularity. This is especially the case for vascular dementia, as current criteria of require evidence of cerebrovascular disease on imaging (NINDS-AIREN).[16] Any study assessing the risk of progression to at least vascular dementia might consequently suffer from some degree of circularity. However, we feel that the influence of this circularity is limited, as the clinical diagnosis of the specific dementia types was fundamentally based on the clinical picture and not on MRI. Unfortunately, we have no neuropathological confirmation of our diagnoses and it must be noted that patients with dementia frequently have shown multiple brain pathologies.[36] We demonstrated in this study that patients with vascular abnormalities on baseline MRI were more likely to develop non-Alzheimer dementia, mostly VaD. Still, it is conceivable that a large proportion of patients in fact suffered from mixed disease. Future research incorporating neuropathological confirmation is needed to answer this question. Another limitation is the absence of clinical characterization of the MCI cases into subgroups (amnestic/non-amnestic, single domain/multiple domain).[37] The clinical subtype may be related to the type of dementia (AD versus non-Alzheimer dementia) a MCI patient is most likely to progress to. Future research should be aimed to find out if the MRI determinations (of atrophy and cerebrovascular disease) add predictive value over this clinical MCI characterization. Compared to the conversion rate of 12% per year reported by Petersen et al, the conversion rate of almost 25% in our group of MCI patients seems rather high. However, our results are comparable to the conversion rate of other memory clinics,[38, 39] while the conversion rate reported by Petersen et al was found in a general community setting.
A strong element is the exploration of the influence of a broad range of vascular abnormalities on MRI, including infarcts, WMH, lacunes and microbleeds. We adjusted analyses for age and sex, and additionally for MMSE and MTA without essential change of the results. Furthermore, we included more MCI patients than most previous reports, including a considerable number of patients who progressed to non-Alzheimer dementia. However, the group of sixteen patients was not large enough to allow examination of progression to specific dementia types other than AD. To conclude, in the clinical setting of a memory clinic, one should be aware of cerebrovascular disease as it appears to be an important predictor of progression to non-Alzheimer dementia.

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3.2 Small vessel versus large vessel vascular dementia: risk factors and MRI findings

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Abstract

Objective

The aim of this study was a cross-sectional comparison of clinical and MRI characteristics and risk factor profiles between patients with small vessel disease (lacunes and white matter hyperintensities) and large vessel disease (large territorial or strategical infarcts) in a large cohort of VaD patients.

Methods

Patients with VaD (NINDS-AIREN) were included in a large multicenter treatment trial (the VantagE study). All patients were examined by a neurologist and interviewed about their medical history. Based on MRI, patients were classified as having large vessel VaD, small vessel VaD, or a combination. Other MRI characteristics included white matter hyperintensities (WMH), medial temporal lobe atrophy (MTA) and general cortical atrophy.

Results

Of the 706 patients, 522 (74%) had small vessel disease, 126 (18%) had large vessel disease and 58 (8%) had both. Patients with small vessel disease were older and less educated, and showed more cortical and medial temporal lobe atrophy than patients with large vessel disease. The most prevalent vascular risk factors (hypertension, diabetes and smoking) were equally distributed between the different types of VaD. However, patients with large vessel disease had more hypercholesterolemia and cardiac risk factors compared to patients with small vessel disease.

Conclusion

Cerebrovascular disease underlying VaD consists in the majority of small vessel disease and in about one fifth of large vessel disease. This study demonstrates heterogeneity between these two groups with regard to risk factor profile and atrophy scores on MRI.

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Introduction

Vascular dementia (VaD) is caused by cerebrovascular disease. Traditionally, VaD has been recognized to develop after multiple strokes. The name 'multi-infarct dementia' became synonymous with all dementias of vascular origin,[1] incorrectly implying that multiple brain infarcts are the only cause of VaD. Currently, the criteria of the National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et al'Enseignement en Neurosciences (NINDS-AIREN) are the diagnostic criteria which are most often used in VaD studies.[2] According to those criteria, neuroimaging is required to demonstrate cerebrovascular disease. The radiological standards define both topographic and severity criteria. Evidence for cerebrovascular disease sufficient for the diagnosis of VaD includes large vessel and small vessel disease. Large vessel disease includes large territorial or strategic infarcts, while small vessel disease consists of lacunes, white matter changes or bilateral thalamic lesions.

At present, both small vessel and large vessel disease may be sufficient for the diagnosis of VaD. However, little is known about the relative prevalence of small vessel and large vessel disease in VaD and their specific underlying cerebrovascular disease, or about their relation with neurodegenerative changes as observed on MRI. Medial temporal lobe atrophy (MTA) is a widely used marker of neurodegeneration, specifically in Alzheimer's disease (AD),[3, 4] but it is also observed in other dementias, including VaD.[5-7]

Several studies have investigated determinants of VaD, and a number of risk factors have been identified. In addition to age,[8, 9] vascular risk factors such as history of stroke,[8, 10, 11] hypertension,[11-13] diabetes,[11, 14] hyperlipidaemia,[15] smoking [16] and cardiac risk factors [8, 9] have been reported. We hypothesized that heterogeneity in cerebrovascular damage underlying VaD would be related to heterogeneity in risk factor profile.

The aim of this study was to determine the relative frequency of small vessel and large vessel disease in a large cohort of VaD patients enrolled into a multicenter randomized trial, and to compare MRI characteristics and risk factor profile dependent on type of vascular damage.

Methods

Study design and patients

Baseline data of 706 patients aged 50-85 years, included in the VantagE study, were used. The VantagE study was a large multicenter, phase III, prospective, randomized, double-blind clinical trial on the effects of rivastigmine in patients with VaD (Novartis International AG, Basel, Switzerland). Trial inclusion criteria included both fulfilment of the DSM-IV diagnostic criteria for VaD and fulfilment of the NINDS-AIREN criteria for probable VaD.[2] The NINDS-AIREN criteria for probable VaD were slightly modified: If neuroimaging criteria for subcortical VaD were met as assessed by the central neuroradiologist, patients were not required to have evidence of a temporal relationship between the dementia syndrome and the evidence of cerebrovascular disease (i.e. these patients were permitted to enter the study with a clinical diagnosis of possible VaD by NINDS-AIREN criteria).[2, 17] Excluded from entry into the study were patients with a history of stroke within the 3 months prior to baseline unless the patient was considered to have fully stabilized in function; a current diagnosis of any primary neurodegenerative disorder; and a current diagnosis of major depression. As well patients with space-occupying lesions or lobar haemorrhages were excluded. All patients gave written informed consent. The study was approved by local Ethics Committees.

Baseline clinical assessment

Diagnostic evaluation included complete medical history (including family history and medication intake), physical and neurological examination, laboratory tests, extensive neuropsychological testing including Mini-Mental State Examination (MMSE)[18] and MRI of the brain. Patients had to have a MMSE score of 10-24 to be included in the study.

Vascular risk factors were determined by history taking as well as physical examination. The following variables were included in the analyses: a history of hypertension (yes/no), diabetes mellitus (yes/no),

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hypercholesterolemia (yes/no), current smoking status (yes/no), and a history of one of the following angina/myocardial infarct (yes/no), atrial fibrillation (yes/no), congestive heart disease (yes/no), heart valve disorder (yes/no), carotid stenosis (yes/no), or peripheral vascular disease (yes/no). Patients were asked about their medication use concerning anti-hypernsive medication, diabetic medication and cholesterol lowering drugs. Blood pressure was measured and the mean value of two measurements on the right arm in supine position at two different occasions was used in the analysis. Blood samples were taken to determine (among others) mean random glucose (mmol/L) and cholesterol (mmol/L) levels. In addition, family history was taken concerning dementia, strokes, cardiac vascular disease and peripheral vascular disease.

MRI protocol

All patients underwent MRI examination before randomization. MRI scanners operating between 0.5 and 1.5 Tesla were used. Axial spin-echo T2-weighted images (T2-WI; echo time [TE]: 80 to 120 ms; repetition time [TR]: 3000 to 4000 ms; slice thickness=5 mm); axial fluid-attenuated inversion recovery (FLAIR) images (TE: 110 to 150 ms; TR: 9000 to 10000 ms; inversion time: 2000 to 2200 ms; slice thickness=5 mm); and axial, sagittal, and coronal spin-echo T1-weighted images (T1-WI; TE: 11 to 20 ms; TR: 500 to 700 ms; slice thickness=5 mm) were acquired.

Image assessment

Image assessment was performed centrally at the Image Analysis Center (VU Medical Center, Amsterdam, the Netherlands) by agreement of two experienced readers blinded to clinical information, with the use of digital image files. The assessment of vascular abnormalities included the items of the radiological NINDS-AIREN criteria for VaD, according to operational definitions earlier proposed (see table 1).[19] Based on these criteria, patients were classified as having large vessel VaD, small vessel VaD, or a combination. For the fulfilment of large vessel disease both a topography and a severity criterion for large vessel disease had to be met. In case of small vessel disease, for white matter hyperintensities (WMH) both topography and severity criteria had to be met, for multiple lacunes and bilateral thalamic lesions only the topography criterion was sufficient. The degree of WMH severity was rated visually on axial FLAIR images using the Age Related White Matter Changes (ARWMC) scale.[20] In short, WMH are ill-defined hyperintensities of >5mm, rated on a 4-point scale ranging from 0 (no lesions) to 3 (diffuse involvement of the entire region), within 5 regions of the brain bilaterally. Here, we used the total degree of WMH (range 0-30) by summing the region-specific scores of both hemispheres. With respect to the WMH criteria for small vessel disease, we used the ARWMC scale to define involvement of 25% of the total white matter (at least twice a score of 2 and twice a score of 3 in the frontal and parieto-occipital regions). A lacune was defined as a lesion with a diameter of ≥ 3mm, with CSF like intensity on all sequences on MRI surrounded by white matter or subcortical gray matter. A paramedian thalamic infarction was defined as: an infarct extending into the paramedian part (defined as extending to the third ventricle) of the thalamus; the extension may be limited to the gliotic rim of the infarct that surrounds the parenchymal defect. All other thalamic lesions with a diameter of ≥3mm were considered as 'thalamic lesions'. Lesions in the thalamus do not always have the same intensity as CSF on all sequences (for example not always on the T1), therefore it was decided to use the term 'lesions', to include both thalamic lacunes and thalamic non-lacunar lesions. All 'thalamic lesions' were regarded as small vessel disease, in contrast to paramedian thalamic infarcts which were regarded as large vessel disease of the posterior cerebral artery. In addition, care was taken to review thalamic lesions and infarcts on T2 weighted images as they can easily been missed on the FLAIR.[21] Further MRI evaluation included MTA on coronal T1-weighted images using the Scheltens scale (possible range of scores: 0 to 4),3 and global cortical atrophy (GCA) on axial FLAIR images (possible range of scores: 0 to 3).[22]

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Statistical analysis

Statistical analysis was performed by means of SPSS 12.0 (SPSS Inc). For comparison of data between the different types of VaD (small vessel disease, large vessel disease or a combination) chi-square tests were used for dichotomous outcome variables. For continuous data we used analysis of variance (ANOVA) with post hoc Bonferroni tests, with age and sex as covariates. Associations between the MRI measures were assessed using partial correlations, controlling for age and sex. Basic associations between the types of VaD and risk factors were assessed in unadjusted analyses using chi-square tests. Subsequently, we used logistic regression models with the risk factors as dependent variables, and the different types of VaD as categorical covariate, controlling for age and sex.

Table 1; Classification of large vessel disease and small vessel disease, based on NINDS-AIREN criteria for VaD2

Large vessel disease	
1. Topography—radiological lesions associated with dementia include any of the following or combinations thereof:	
Anterior cerebral artery	Bilateral
Posterior cerebral artery, including	Paramedian thalamic infarcts
	Inferior medial temporal lobe lesions
Association areas	Parietotemporal
	Temporo-occipital
	Angular gyrus
Watershed carotid territories	Superior frontal
	Parietal region
2. Severity—in addition to the above, relevant radiological lesions associated with dementia include:	
Large vessel lesions of the dominant hemisphere	
Bilateral large vessel hemispheric strokes	
Small vessel disease	
1. Topography	
Multiple basal ganglia and frontal white matter lacunes	
Extensive periventricular white matter lesions	
Bilateral thalamic lesions	
2. Severity	
Leukoencephalopathy involving at least 1/4 of the total white matter	

Classification of large and small vessel disease according vStraaten et al.[19]

Results

The total study population involved 706 patients with VaD, with a mean age of 73 years (SD 8), and an overrepresentation of men (63%) (table 2). The patients were mildly-to-moderately demented with a mean MMSE score of 19 (SD 4). Of the 706 patients, 522 (74%) had small vessel disease, 126 (18%) had large vessel disease and 58 (8%) had both. Patients with small vessel disease were older and less educated than patients with large vessel disease. The MMSE was comparable in patients with small and large vessel disease; however, patients with a combination of small and large vessel disease had a lower MMSE.

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Inspection of specific MRI abnormalities in patients with small vessel disease (n=522) revealed that small vessel disease was for the largest part attributable to extensive WMH (the diagnosis of VaD was based solely on WMH in 40% of the patients) (figure 1). Small vessel disease based on either lacunes (6%) or thalamic lesions (9%) without additional occurrence of WMH was rare. A combination of different forms of small vessel disease was observed in 45% of the patients. The majority of patients with large vessel disease (n=126) showed just one type of infarct (71%). Two types of infarcts were shown in a quarter of the patients (27%), and the presence of three types of infarcts was rare (2%). The majority of infarcts were shown in an association area of the medial cerebral artery (MCA) (n=64) or in a watershed area of the carotid territories (n=56) (figure 2). Infarcts in the territories of the posterior cerebral artery (PCA) were demonstrated less frequently (n=40). Bilateral infarcts of the anterior cerebral artery (ACA) were uncommon (n=4), and never occurred without an additional large vessel infarct. Examination of patients with a combination of small and large vessel disease (n=58) showed more or less the same distribution of types of infarct as patients with only large vessel disease. However, inspection of the different forms of small vessel disease in this combination group showed more bilateral thalamic lesions compared to patients with only small vessel disease.

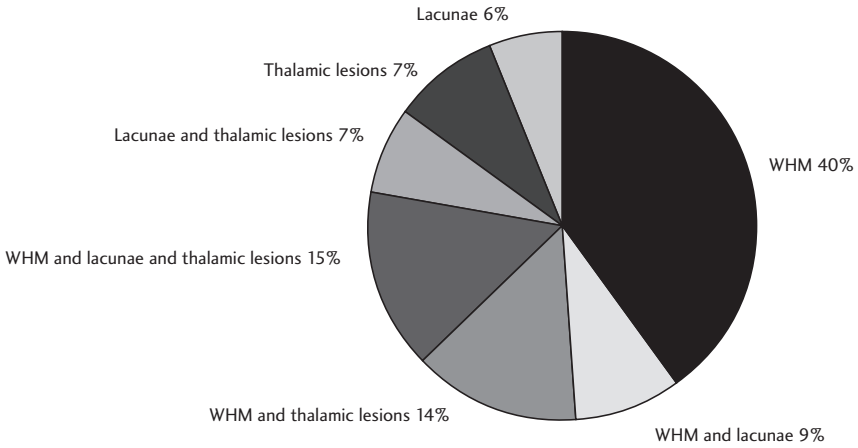

Figure 1;

Distribution of different forms of small vessel disease.

Within the group of small vessel disease (n=522), patients were categorized to have extensive periventricular white matter lesions involving at least 1/4 of the total white matter (WMH)), bilateral thalamic lesions (thalamic lesions), multiple basal ganglia and frontal white matter lacunes (lacunes), or a combination thereof. Data presented as percentage of patients with small vessel disease demonstrating these different forms of small vessel disease.

Examination of other MRI abnormalities showed, as expected, that patients with small vessel disease had more WMH than the large vessel group, with the combination group in between. Patients with small vessel disease showed in 8% of cases a cerebral infarct on MRI (note that a larger proportion of patients had infarcts, as infarcts in the non-dominant hemisphere do not lead to a diagnosis of large vessel VaD). Both cortical atrophy and MTA were more severe among patients with small vessel disease compared to patients with large vessel disease (table 2). Adjusted for age and sex, the presence of a cerebral infarct was marginally negatively correlated to cortical atrophy (partial r= - 0.16, p<0.001), whereas the presence of multiple lacunes and severity of WMH were both positively correlated to cortical atrophy (partial r=0.18, p<0.001 and r=0.12, p =0.001). Correlations between vascular MRI abnormalities and MTA were poor (cerebral infarct: partial r= -0.08, p=0.03, lacunes: partial r= -0.04, p=0.28, and WMH: partial r=0.08, p=0.03).

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In the total group, hypertension was the most prevalent risk factor (80%), followed by hypercholesterolemia (39%), diabetes (26%) and smoking (20%) (table 3). Hypercholesterolemia was more often present in patients with large vessel disease compared to patients with small vessel disease, with the combination group in between. The presence of the other three most prevalent risk factors was equally distributed between the different types of VaD. Patients with large vessel disease used more often cholesterol lowering drugs compared to patients with small vessel disease. Mean random glucose and cholesterol levels, as well as blood pressure measurements, were not different between the types of VaD. Cardiac risk factors (history of angina/myocardial infarct, atrial fibrillation, congestive heart disease, heart valve disorder) and carotid stenosis were more frequently present in patients with large vessel disease compared to patients with small vessel disease. The presence of peripheral vascular disorder did not differ between the subgroups. Patients with large vessel disease or a combination of small and large vessel disease had a higher prevalence of family history of cardiac disease compared to patients with small vessel disease. A family history of dementia was infrequently reported by patients in the combination group, but its presence in patients with small or large vessel disease was comparable (one out of four).

Table 2; Characteristics

	Small vessel disease	Large vessel disease	Small & large vessel disease	
Number of patients	522	126	58	
Demographics				
Age (years)	73 (8)	71 (8)a	72 (8)	p<0.05
Sex n (%men)	314 (60%)	84 (67%)	42 (72%)	ns
Education (years)	9.0 (4.0)	10.7 (3.7)[a]	9.4 (3.8)	p<0.001
MMSE	19.2 (3.8)	18.6 (4.1)	17.5 (4.0)[a]	p<0.01
MRI				
ARWMC[1]	16.5 (4.9)	6.5 (4.3)[a, c]	13.6 (5.5)[a]	p<0.001
Cortical atrophy	1.5 (0.8)	1.2 (0.8)[a]	1.4 (0.8)	p<0.001
MTA[2]	1.7 (0.9)	1.4 (1.1)[a]	1.7 (0.9)	p=0.001

Values are expressed as mean (standard deviation) unless stated otherwise. ANOVA's with age and sex as covariates and post-hoc Bonferroni tests were performed.
1: data missing of 2 patients
2: data missing of 12 patients
a = significant difference compared to patients with small vessel disease;
b = significant difference compared to patients with large vessel disease;
c = significant difference compared to patients with both small and large vessel disease.
Abbreviations: MMSE: Mini-Mental State Examination (0-30); ARWMC: age related white matter changes (0-30) MTA: medial temporal lobe atrophy (0-4).

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Table 3; Risk factors

	Total group (n=706)	Small vessel (n=522)	Large vessel (n=126)	Small & large vessel (n=58)	Overall, unadjusted
Medical history					
Smoking (current)	144 (20)	105 (20)	27 (21)	12 (21)	ns
Hypertension	562 (80)	410 (79)	105 (83)	47 (81)	ns
Diabetes	184 (26)	129 (25)	37 (29)	18 (31)	ns
Hypercholesterolemia	270 (39)	176 (34)b,c	68 (54)	26 (45)	p<0.001
Angina/myocardial infarct	125 (18)	72 (14)	39 (31)[a]	14 (24)	p<0.001
Atrial fibrillation	75 (11)	41 (8)	29 (23)[a, c]	5 (9)	p<0.001
Congestive heart disease	36 (5)	22 (4)	13 (10)[a]	1 (2)	p<0.01
Heart valve disorder	28 (4)	14 (3)	11 (9)[a]	3 (5)	p<0.01
Carotid stenosis	68 (10)	39 (8)	25 (21)[a, c]	4 (7)	p<0.001
Peripheral vascular disease	59 (8)	38 (7)	14 (11)	7 (11)	ns
Medication use					
Hypertension	490 (70)	354 (67)	95 (76)	41 (72)	ns
Diabetes	144 (21)	100 (19)	29 (23)	15 (26)	ns
Hypercholesterolemia	168 (24)	101 (20)b	50 (40)	17 (30)	p<0.001
Blood pressure					
Systolic BP (mm/Hg) mean (SD)	139 (15)	140 (15)	137 (15)	137 (15)	ns
Diastolic BP (mm/Hg) mean (SD)	79 (9)	80 (9)	78 (9)	79 (10)	ns
BP >140/90 mm/Hg	298 (44)	225 (44)	51 (43)	22 (39)	ns
Blood samples					
Random glucose (mmol/L) mean(SD)	6.6 (2.7)	6.6 (2.7)	6.6 (2.7)	6.5 (2.6)	ns
Cholesterol (mmol/L) mean (SD)	5.3 (1.1)	5.4 (1.1)	5.2 (1.2)	5.3 (1.0)	ns
Family history					
Dementia	164 (24)	124 (25)[c]	34 (28)[c]	6 (11)	p<0.01
Strokes	226 (34)	160 (33)	46 (38)	20 (35)	ns
Cardiovascular disease	201 (30)	129 (26)	50 (42)[a]	22 (38)	p<0.01
Peripheral vascular disease	63 (10)	46 (10)	11 (10)	6 (12)	ns

Data given as number (percentage) unless otherwise specified. BP = blood pressure. Data given as number (percentage) unless otherwise specified. BP = blood pressure.
Comparison of data between the different subgroups was performed for continues variables using t-tests and for dichotomous variables first using chi square tests, second, using logistic regression models controlling for age and sex. Meaning of letters: comparison between groups adjusted for age and sex;
a = significant difference compared to patients with small vessel disease; p<0.01
b = significant difference compared to patients with large vessel disease; p<0.001
c = significant difference compared to patients with both small and large vessel disease; p<0.05.

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Discussion

In this large cohort of VaD patients we demonstrated that the diagnosis of VaD was in three-quarter of the patients (74%) based on small vessel disease, compared to almost one fifth of the patients (18%) who fulfilled the criteria for large vessel VaD and one out of ten patients (8%) who fulfilled criteria for both types of VaD. Patients with small vessel disease showed more cerebral atrophy, as shown by higher scores of MTA and cortical atrophy. By contrast, large vessel disease seemed to be associated with hypercholesterolemia and cardiac disease.

Few other studies have examined the relative prevalence of small vessel and large vessel disease in VaD.[23, 24] A study performed in patients with vascular dementia and patients with Alzheimer's disease combined with cerebrovascular disease, reported a relative prevalence of 64% of extensive WMH, 40-47% of lacunes, and 39-46% of infarcts, percentages comparable to our results.[25] A cohort of 68 Asian, male VaD patients demonstrated a relatively high frequency of small vessel disease that was similar to the current study.[24] However, in contrast to findings in the current study where the majority of small vessel disease consisted of WMH, the high prevalence of small vessel disease in this Asian cohort was due to a large amount of lacunes, possibly related to genetic factors. In agreement with our results, a previous neuropathological study supports the view that small vessel disease is the main substrate relevant in VaD, after comparing brains with vascular disease of demented and non-demented patients.[26]
The prevalence of WMH only was remarkably high in the present study. In the whole cohort, 58% of the patients showed WMH sufficient for the criteria of small vessel disease.[2] WMH are not specific for VaD, but also commonly present in non-demented individuals and in AD patients.[27-30] However, compared to healthy elderly or other types of dementia, the pattern of WMH in VaD by definition is extensive.[28] Involvement of at least 25% of the total white matter is considered sufficient for a diagnosis of VaD related,[31, 32] although this percentage was set purely arbitrarily. Moreover, application of this threshold is also debatable. In the present study the threshold was defined using the ARWMC score,[19] however, for example volumetric assessment of WMH might have yielded more accurate measures.

In our sample VaD patients had moderate to severe MTA and cortical atrophy on MRI. Although more severe among patients with small vessel disease, both MTA and cortical atrophy were also observed in patients with large vessel VaD. This is in accordance with earlier studies which demonstrated more severe MTA in VaD patients compared to controls.[5-7] There are several possible explanations for the relation between cerebrovascular disease and neurodegenerative changes. First, MTA and cortical atrophy as observed in VaD may be due to coexisting AD or even to misdiagnosis, patients actually suffering AD.[33, 34] Although with lack of neuropathological confirmation we cannot exclude this possibility, all our patients were carefully diagnosed by the clinical and radiological NINDS-AIREN criteria for VaD.[2] To fulfil the NINDS-AIREN criteria, cerebrovascular disease has to be shown on neuroimaging (other criteria like DSM-III, ICD-10 and DSM-IV do not require neuroimaging). Furthermore, a neuropathological study showed for the NINDS-AIREN criteria a low sensitivity, but a high specificity excluding 91% of patients with Alzheimer's disease.[35] Second, a synergistic interaction between degenerative and vascular lesions has been suggested.[33, 36, 37] Third, neurodegenerative changes may be secondary to vascular disease, due to e.g. ischemia or Wallerian degeneration. However, the design of our study prevented us from drawing conclusions on causality of the associations we found. Future research projects using more sophisticated and modern measures can help to identify possible concomitant AD in VaD patient groups. Additionally, further research in this field is necessary to determine the underlying relation between atrophy and cerebrovascular disease.

Hypertension was the most prevalent risk factor, with a prevalence of 80 percent in the whole cohort. Previously the presence of hypertension has been found to triple the risk of VaD,[38] reflecting the importance of this risk factor. The prevalence of hypertension was similar in patients with small vessel and large vessel disease, as were other highly prevalent risk factors such as diabetes and smoking. In contrast, hypercholesterolemia, although of high prevalence in small vessel disease (one third of the patients), was even almost twice as prevalent in patients with large vessel disease. Additionally, cardiac risk factors and a history of carotid stenosis were more often present in patients with large vessel disease

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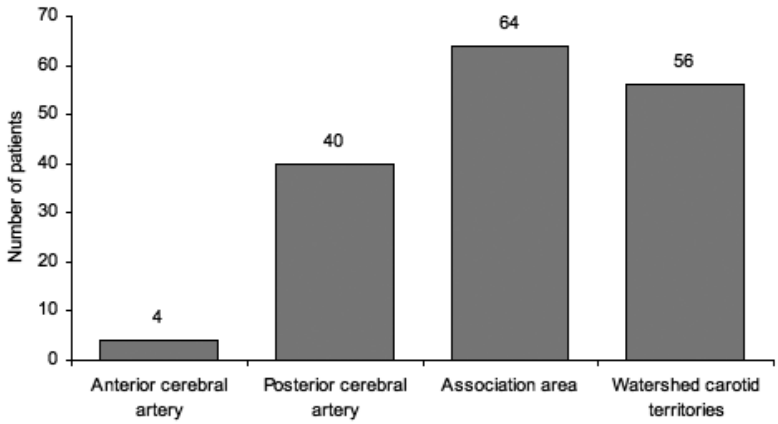

Figure 2; Distribution of different (location) types of large vessel infarction.
Patients with large vessel disease (n=126) were categorized to the location criteria of large vessel disease; bilateral infarction of the anterior cerebral artery, infarctions in the territory of the posterior cerebral artery, infarction in an association area of the medial cerebral artery or infarction in the watershed area of the carotid territory. Here, data are presented as number of patients demonstrating the different types of large vessel infarction, regardless of fulfilment of severity criteria. If patients presented more then one large vessel infarction, both types are demonstrated.

compared to patients with small vessel disease. This combination of large vessel VaD and cardiac risk factors and carotid stenosis is in line with the associations between these risk factors and large vessel stroke without dementia.[39, 40] A study comparing the risk factor profile in patients with small vessel and large vessel disease without dementia, found in accordance with our results a higher prevalence of hypercholesterolemia and myocardial infarct in patients with large vessel disease. However, in contrast to the comparable prevalence of hypertension we found in both patient groups, they reported a higher prevalence of hypertension in patients with small vessel disease.41 Although several studies have examined risk factors in patients with VaD,8-16 the difference in risk factor profile according to type of cerebrovascular disease in VaD has seldom been demonstrated. To our knowledge, only one neuropathological study investigated cardiovascular disease in small vessel and large vessel VaD. In agreement with our results, they found cardiovascular features consistently more often in the large vessel compared to the small vessel group.[42]

Strengths of the present study include the large study population, as it is one of the largest clinical series of patients affected by VaD to date. A limitation results from the study design (a treatment trial), which could have had an effect on the inclusion of patients and limits the possibility to generalize the results to the VaD patient group as a whole. Patients had to be able to undergo extra examinations, probably resulting in the exclusion of patients with severe vascular disease. However, this would have held for participation in any study, not only clinical trials. Furthermore, we cannot exclude the possibility of misdiagnosis. However, all patients were carefully screened for fulfilment of the clinical and radiological NINDS-AIREN criteria for VaD,[2] generally considered accurate criteria. Nonetheless, this could also imply a limitation, since the NINDS-AIREN criteria have been shown not to be interchangeable with other diagnostic methods for VaD,[43] which requires caution when comparing these results to other studies. Another limitation is the definition of risk factors. In some countries all patients with stroke regardless of their cholesterol level are put on statin therapy, therefore the data about use of cholesterol lowering medication should be interpret with care. Furthermore, although all patients underwent the same diagnostic evaluation, there was no extensive cardiovascular work-up and therefore probably a certain amount of not yet known cardiovascular disease was missed. In stroke studies small and large vessel

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disease is often classified according to the TOAST criteria.[44] It can be useful in future studies of vascular dementia to use these classification, especially to be able to make a differentiation between large vessel disease caused by large vessel atherosclerosis and cardioembolism.

In conclusion, we found that the majority of cerebrovascular damage in VaD consists of small vessel disease, and that this small vessel disease is mostly WMH. In addition, we showed that patients with VaD show moderate MTA and cortical atrophy, the severity of the atrophy being higher in patients with small vessel disease compared to patients with large vessel disease. In contrast, patients with large vessel disease have more cardiac risk factors compared to patients with small vessel disease.

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Part 4

Neurological signs in dementia in relation to MRI measures

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extrapyramidaal systeem' alle hersendelen buiten de piramidebaan. De piramidebaan is de grote uitvalsweg die vanuit de motore hersenschors bewegingsopdrachten doorgeeft om de spieren te activeren, zodat de geplande beweging daadwerkelijk uitvoert wordt. Toen men ontdekte dat prikkeling van andere hersendelen dan de piramidebaan ook tot beweging kon leiden, noemde men die gebieden het extrapiramidale systeem.

Uit Kramers Nederlands woordenboek & www.wikipedia.com

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4.1 Neurological signs in relation to white matter hyperintensities in memory clinic patients

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Abstract

Purpose
To determine the frequency of neurological signs in a memory clinic population and to explore their associations with white matter hyperintensity (WMH).

Methods
We included patients with Alzheimer disease (AD; n=210), vascular dementia (VaD; n=34), mild cognitive impairment (MCI; n=86) and subjective complaints (n=153). Presence of extrapyramidal and unilateral signs was assessed from medical charts. On MRI, WMH volumes were extracted automatically.

Results
Extrapyramidal signs were found in 10% and unilateral signs in 12% of the patients. Age and sex adjusted, extrapyramidal signs occurred more often in VaD compared to patients with subjective complaints. Unilateral signs were more prevalent in all groups compared to patients with subjective complaints. Two-way ANOVA with WMH as dependent variable showed a main effect of diagnosis ($p<0.001$), but not of extrapyramidal signs ($p=0.62$). In contrast, two-way ANOVA showed main effects of diagnosis ($p<0.001$) and unilateral signs ($p=0.001$). Furthermore, there was an interaction between these factors ($p=0.04$); if unilateral signs were present, patients with subjective complaints and VaD showed more WMH, whereas there was no relation in AD and MCI.

Conclusion
Extrapyramidal and unilateral signs are common in memory clinic patients, but are only modestly related to WMH.

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Introduction

Neurological signs have been related to dementia.[1-3] In patients with dementia the presence of neurological signs has been associated with a worse prognosis.[2, 4, 5] Little is known, however, about the relative frequency of neurological signs in different dementia stages and types, or about their underlying neuropathological substrate.

Alzheimer's disease (AD) is the most common form of dementia. AD patients have shown a high frequency of primitive reflexes (41%),[4] cranial nerve signs (23%),[2] and extrapyramidal signs (12%-30%).[2, 4, 6, 7] Furthermore, neurological signs and especially extrapyramidal signs showed rapid progression over time and were more prevalent in more severe AD cases[2, 7] Although current criteria of vascular dementia (VaD) require the presence of neurological signs,[8] little is known about their frequency. Research showed that VaD patients in general demonstrate a number of signs, including both unilateral signs (e.g. reflex asymmetry, hemimotor dysfunction) and extrapyramidal signs (e.g. rigidity, hypokinesia).[2, 9] The term mild cognitive impairment (MCI) is used to characterize patients with mild cognitive deficits not sufficient for the diagnosis of dementia.[10] It is known that a substantial proportion of MCI patients will ultimately develop dementia. Research on neurological signs in MCI is scarce. Three studies, of which two were only directed at extrapyramidal signs, found the frequency of most neurological signs in MCI to be higher than in subjects without cognitive impairment but lower than in dementia.[11,12, 13] In addition, extrapyramidal signs were related to the severity of cognitive impairment and an increased risk of progression to AD. Comparative studies into neurological signs in the various diagnostic groups of AD, VaD and MCI are few and due to methodological differences the studies are often difficult to compare. Furthermore, most research has focussed on extrapyramidal signs, and other neurological signs, like hemimotor dysfunction, reflex asymmetry or hemianopia were often not taken into account.

The origin of neurological signs in dementia is not entirely clear. It is not known whether these signs for example reflect age-associated changes or if they are the result of degenerative abnormalities. Associations between extrapyramidal signs and substantia nigra pathology have been suggested in AD.[14, 15]Others hypothesize that vascular pathology may play a role.[16] On brain MRI, white matter hyperintensities (WMH) are regarded as suggestive of vascular pathology and considered to reflect ischemic damage to the brain.17 WMH have been related to decreased gait performance,[18] and associations with extrapyramidal signs in elderly have been suggested.[19-21] In VaD patients, WMH appeared to be related to rigidity, parkinsonian type gait disorder, dysarthria and dysphagia.[9] Additionally, at least one unilateral sign was found in three-quarter of the more than 500 patients with small vessel VaD.[9] The role of WMH in relation to neurological signs in MCI or AD patients has not been studied.

Considering the expected frequency and consistency of assessments we decided to focus on extrapyramidal signs and unilateral signs, leaving out some other neurological signs such as primitive reflexes. The primary aim of our study was to determine the frequency of extrapyramidal signs and unilateral signs in a large cohort of patients attending a memory clinic, expecting to find a higher frequency of signs in patients with dementia compared to non-demented subjects. Secondly, we determined presence of WMH in this population and studied whether patients with extrapyramidal signs or unilateral signs showed a larger volume of global WMH, hypothesizing that ischemic vascular damage plays a role in the presence of these signs in dementia.

Methods

Patients

We consecutively included patients (n=519) who attended our outpatient memory clinic between April 2004 and September 2007 and who were subsequently diagnosed with AD, VaD or MCI or if clinical investigations showed no abnormalities. All patients visiting our memory clinic are investigated by a standardized diagnostic work-up. Standardized assessment included medical history, physical and neurological examination, laboratory tests, neuropsychological testing including Mini-Mental State Examination (MMSE), electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain.

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Subsequently, diagnoses are made in a multidisciplinary consensus meeting according to widely used clinical criteria. For the diagnosis of AD the criteria of the National Institute on Neurological and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA)[22] were used, and VaD was diagnosed by use of criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN).[8] MCI was diagnosed according to the Petersen-criteria.[10] When all clinical investigations were normal (ie, MCI criteria were not fulfilled), patients were considered to have subjective complaints. The study was approved by the local Medical Ethical Committee. All patients gave written informed consent for their clinical data to be used for research purposes.

Neurological signs

The medical notes of the first neurological examination were reviewed retrospectively to assess the presence of neurological signs. In this study we used only the data concerning unilateral signs and extrapyramidal signs. Unilateral signs were regarded to be present, if one or more of the following signs were found at neurological examination: (1) hemimotor dysfunction, defined as any asymmetry in muscle tone or strength of extremities, (2) hemisensory dysfunction, not scored if there was an overt peripheral neuropathy or when a sensory deficit was caused by a former surgery, (3) hemianopsia, (4) reflex asymmetry, scored only if there was clear asymmetry of more than one deep tendon reflex, (5) Babinski sign, and (6) hemiplegic gait. Extrapyramidal signs were regarded to be present if one or more of the following signs were found at neurological examination: (1) rigidity, scored when the notes mentioned rigidity, cogwheel phenomenon or increased muscle tone without indications of increased reflexes, (2) hypokinesia, scored when the notes mentioned hypokinesia, bradykinesia, decreased arm swing or facial rigidity, (3) Parkinsonian resting tremor and (4) Parkinsonian gait, defined as a slow gait with shuffling steps, decreased arm swing, stooped posture and difficulty turning. All signs were rated as 'absent' or 'present', and as such used in the data analyses.

APOE

APOE genotype was determined, isolating DNA from 10 ml EDTA blood by the QIAamp DNA blood isolation kit from Qiagen. The genotype was determined with the Light Cycler APOE mutation detection kit (Roche Diagnostics GmbH, Mannheim, Germany). Subjects were classified as APOE e4 non-carriers or carriers of at least one APOE e4 allele.

MRI protocol

All patients underwent MRI of the brain. The scan had to be performed at the same day (n=442) or within one year after baseline neurological examination (n=77; median time difference[interquartile range] = 1.7[1.0-2.9] months) to be included in the study. MRI was performed on a 1.0 Tesla machine (Magnetom Impact Expert Siemens AG, Erlangen, Germany) following a standard protocol, including coronal T1-weighted 3D MPRAGE (magnetization prepared rapid acquisition gradient echo; 168 slices, field of view [FOV] 250mm, matrix 256x256, slice thickness 1.5mm, echo time [TE]: 7ms, repetition time [TR]: 15ms, inversion time [TI] 300ms, flip angle 15°) and axial FLAIR (fluid attenuated inversion recovery, 17 slices, FOV 250mm, matrix 256x256, slice thickness: 5mm, interslice gap: 1.5mm, TE: 105ms, TR: 9000ms, TI 2200ms, flip angle 180°) and axial spin-echoT2-weighted images (21 slices, FOV 250mm, matrix 512x512, slice thickness 5mm, interslice gap 1.5mm, TE 119ms, TR 5775ms, flip angle 180°).

WMH volumes

First, image quality was assessed using visual inspection to exclude images with movement artefacts (n=3). Furthermore, we excluded images with intracerebral pathology (tumor; n=1). Then, WMH volumes were determined on the remaining scans (n=515). WMH volumes were automatically extracted following the method previously described in.[23, 24] Briefly, an intracranial mask is created based on the automatic template based segmentation of the T2 images. The white matter (WM), grey matter, and cerebrospinal fluid (CSF) templates are automatically mapped on the T2 image. Next, the T2 and FLAIR images are automatically co-registered, and the CSF segmentation is finalized (taking into account both the FLAIR and the T2 signal intensities).25 Intracranial (IC) volumes and parenchyma volumes (= IC − CSF volume)

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were automatically extracted. As described before,[25] the automatic WMH segmentation is based on a Fuzzy interference system, which uses linguistic variables to classify a voxel. Using the Fuzzy C-Means algorithm,[26] each voxel of the FLAIR image was classified according to the voxel signal intensity (DARK, MEDIUM_BRIGHT and BRIGHT) and according to the voxel position (guided by the mapped templates; IC, WM). Unlike in the original method where both T2 and FLAIR signal intensities were considered, in this study the lesions were extracted based on the FLAIR signal intensity only using the following rule: If voxel_position is WM and flair_intensity is BRIGHT then segmented_voxel is WMH.
To optimize the automatic segmentation outcome for our data set, we first created a "gold standard" by manually outlining the WMH in 20 patients. The agreement between the gold standard and the automatic segmentation was maximized by varying the minimum membership degrees of the FLAIR signal intensity to BRIGHT and the voxel position in WM, in a grid search way. The exact volumes of WMH were computed automatically. Infratentorial hyperintensities were not taken into account. Finally, all segmentations were visually inspected to determine if the quality of the segmentation was satisfactory. To do so, mosaic views of all individual segmentation results were generated as overlays on the input images, and side by side with "clean" input images. Errors in the segmentation included misregistration of the maps (n=11) and failure of the WMH segmentation (n=21). After exclusion of these scans, we had WMH volumes of n=483 images available for this study (AD n=210, VaD n=34, MCI n=86, subjective complaints n=153).

Lacunes and infarcts

The presence of lacunes was visually assessed and defined as T1-hypointense and T2-hyperintense CSF-like lesions surrounded by white matter or subcortical grey matter with a minimum diameter of 3mm, not located in areas with a high prevalence of widened perivascular spaces (vertex, anterior commisure). The presence of infarcts was determined using the different MRI sequences.

Statistics

Statistical analyses were performed using SPSS 14.0 for Windows (SPSS Inc). Differences in baseline characteristics between the diagnostic groups were analysed using chi-squared test for dichotomous outcome variables and one-way analysis of variance (ANOVA) for continuous data. For comparison of frequency of neurological signs between diagnostic groups we used logistic regression models, adjusting for age and sex, with the patients with subjective complaints as reference group.
WMH volumes were not normally distributed, therefore WMH volumes were log-transformed (ln[1+WMH volume]). Comparison of WMH volumes between the diagnostic groups was performed using one-way ANOVA with post hoc Bonferroni tests, adjusted for age, sex and intracranial volume. Finally, to examine the relation between diagnosis, presence of neurological signs and WMH volumes we used two-way ANOVA's using WMH volumes as the dependent variable, diagnosis and presence of neurological signs as independent variable and age, sex and intracranial volumes, and additionally lacunes and infarcts, as covariates.

Results

Baseline clinical characteristics are presented in table 1. The mean age at the time of MRI was 67±11 years with 226(47%) women. The mean MMSE was 24±6, with the highest score for patients with subjective complaints and the lowest score for patients with AD and VaD. Of the AD patients 70% showed to have at least 1 APOE e4 allel, in contrast to patients with subjective complaints (31%) and VaD (35%), with the MCI patients in between (54% with at least 1 APOE e4 allel). Of the total population of 483 patients, 50 patients (10%) showed extrapyramidal signs and 60 patients (12%) showed unilateral signs at neurological examination. The most frequently observed extrapyramidal signs included rigidity and Parkinsonian gait disorder. Hemimotor dysfunction and reflex asymmetry were the most frequently observed unilateral signs.

Logistic regression showed that extrapyramidal signs occurred more often in all diagnostic groups compared to patients with subjective complaints (OR's [95% CI] varying from 2.8 [1.0-8.2] for MCI to 12.1 [4.1-36.0] for VaD; table 2). In MCI and AD these effects disappeared after adjustment for age and sex, while the relative frequency of extrapyramidal signs remained high in VaD patients (OR [95% CI]: 5.4

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[1.7-17.3]). Unilateral signs were more prevalent in all diagnostic subgroups compared to patients with subjective complaints (OR's [95% CI] varying from 4.7 [1.6-13.9] for MCI to 18.1 [5.8-55.9] for VaD). These estimates were only slightly attenuated after adjustment for age and sex.

Adjusted for age and sex, total brain fraction was lower in MCI, AD and VaD patients than in patients with subjective complaints. In addition, the brain fraction of AD patients was lower compared to MCI patients. Lacunes and infarcts were most frequently demonstrated by VaD patients, without differences in frequency between AD, MCI and patients with subjective complaints. Total WMH volumes were larger in both AD ($p<0.05$) and VaD ($p<0.001$) compared to patients with subjective complaints and MCI, and VaD patients showed higher WMH volumes compared to AD ($p <0.001$). After additional adjustment for intracranial volume, these results remained essentially unchanged.

Table 1; Characteristics

	Subjective complaints	MCI	AD	VaD	p value
Number of patients	153	86	210	34	
Demographics					
Age (years)	59 (10)	69 (8)	70 (10)	71 (9)	<0.001
Sex n (%women)	79 (52%)	23 (27%)	113 (54%)	11 (31%)	<0.001
MMSE	29 (1)	27 (2)	20 (5)	21 (6)	<0.001
APOE e4 (≥1 allel) n(%)	44 (31%)	38 (54%)	124 (70%)	7 (35%)	<0.001
Neurological signs					
Extrapyramidal signs	6 (4%)	9 (11%)	24 (12%)	11 (33%)	<0.001
Rigidity	4 (3%)	7 (8%)	14 (7%)	9 (27%)	<0.001
Brady/hypokinesia	2 (1%)	5 (6%)	10 (5%)	3 (10%)	0.10
Tremor	2 (1%)	3 (4%)	9 (5%)	4 (12%)	0.03
Parkinsonian gait	0	1 (1%)	9 (5%)	5 (16%)	<0.001
Unilateral signs	5 (3%)	12 (14%)	30 (15%)	13 (38%)	<0.001
Hemimotor dysfunction	4 (2%)	5 (6%)	9 (4%)	6 (18%)	<0.01
Hemisensory dysfunction	1 (1%)	1 (1%)	3 (2%)	1 (3%)	0.71
Hemianopsia	1 (1%)	1 (1%)	5 (3%)	3 (9%)	0.02
Reflex asymmetry	1 (1%)	7 (8%)	12 (6%)	11 (32%)	<0.001
Babinski sign	2 (1%)	5 (6%)	8 (4%)	4 (13%)	0.02
Hemiplegic gait	0	0	1 (1%)	2 (7%)	<0.01

Data presented as mean(SD) or as n(%).Comparison of data using chi-squared test for dichotomous variables and one-way ANOVA for continuous variables.
Missing: APOE e4 status n=73, extrapyramidal signs n=19, unilateral signs n=7.

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Subsequently, we investigated the association between WMH volumes and presence of extrapyramidal signs. Two-way ANOVA with diagnosis and extrapyramidal signs as independent variables and WMH volume as dependent variable showed a main effect of diagnosis ($p<0.001$), but not of extrapyramidal signs ($p=0.62$). Furthermore, there was no interaction between diagnosis and extrapyramidal signs ($p=0.45$), indicating that the difference of WMH volumes in the diagnostic groups was not related to the presence of extrapyramidal signs (figure 1). A different picture emerged looking at unilateral signs. Two-way ANOVA showed a main effect of diagnosis ($p<0.001$) and of unilateral signs ($p=0.001$). In addition, there was an interaction between diagnosis and unilateral signs ($p=0.04$; figure 2). Patients with subjective complaints and VaD patients showed higher WMH volumes if unilateral signs were present compared to patients without unilateral signs, whereas unilateral signs were not related to WMH volumes in AD and MCI patients. These results remained essentially unchanged after additional adjustment for the presence of lacunes and infarcts.

Table 2; Frequency of extrapyramidal signs and signs of lateralization compared to patients with subjective complaints.

	Subjective complaints	MCI	AD	VaD
Extrapyramidal signs				
Model 1	1 (ref)	2.8 (1.0-8.2)	3.2 (1.2-8.1)	12.1 (4.1-36.0)
Model 2	1 (ref)	1.3 (0.4-4.1)	1.6 (0.6-4.3)	5.4 (1.7-17.3)
Unilateral signs				
Model 1	1 (ref)	4.7 (1.6-13.9)	5.0 (1.9-13.2)	18.1 (5.8-55.9)
Model 2	1 (ref)	3.2 (1.0-10.0)	3.7 (1.3-10.3)	12.1 (3.7-39.4)

Data presented as OR (95% CI).
Logistic regression analysis using patients with subjective complaints as reference group, first unadjusted (model 1), second adjusted for age and sex (model 2)

Table 3; Baseline MRI

	Subjective complaints n=153	MCI n=86	AD n=210	VaD n=34
Brain fraction (parenchyma/IC)	0.84 (0.03)	0.81 (0.03)a	0.79 (0.03)a,b	0.79 (0.04)a
Lacunes present n(%)	22 (14%)	16 (19%)	27 (13%)	27 (79%)a,b,c
Infarct present n(%)	5 (3%)	5 (6%)	6 (3%)	12 (43%)a,b,c
WMH volume (ml)	2.1 (5.8)	6.9 (9.9)	9.0 (14.7)a,b	45.6 (31.4)a,b,c

Data presented as n(%) or mean (SD).
Comparison of data between the different subgroups was performed for dichotomous variables using logistic regression controlling for age and sex and for continuous data using ANOVA with post hoc Bonferroni using age and sex as covariate.
Please note that for WMH volumes raw data are presented, while statistical analysis was performed using log-transformed volumes.
Meaning of letters: pairwise groupcomparison adjusted for age and sex ($p<0.05$):
a. compared to subjective complaints; b. compared to MCI; c. compared to AD;

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Discussion

We found that neurological signs are common in a memory clinic population and differed in frequency according to diagnosis. A comparable number of MCI and AD patients showed unilateral (14% and 15%) and extrapyramidal signs (11% and 12%). The frequency of extrapyramidal signs in AD in our study is comparable to most earlier reports.[2, 4, 5] Others found higher frequencies,[6, 7] probably associated with differences in disease severity and assessment methodologies. Concerning MCI patients, our results are comparable to a previous report.[11] A few studies found more signs in MCI compared to cognitively normal people, but contrary to our results, less than in demented individuals.[11-13] A possible explanation is the population based origin of the former studies, while we examined a memory clinic cohort which might have influenced the severity of both MCI and AD.

Strengths of the current study include the large population and the simultaneous examination of different diagnostic groups. Since the presence of neurological signs is known to be influenced by age, all analyses were age-adjusted.[27] Furthermore, we used a validated, fully automatic method to determine WMH volumes. All analyses with WMH were corrected for intracranial volume. An important limitation is the lack of WMH volumes of separate hemispheres or information about possible asymmetric distribution of WMH. On the other hand, WMH is often found bilaterally on MRI. Furthermore, the neuropathology of WMH is known to be heterogeneous and more sophisticated imaging techniques are needed to determine when WMH relates to actual damage (associated with neurological signs).[28] Another important limitation was the use of the clinical neurological examination instead of a standardized rating scale, which may have resulted in an underestimation or overestimation of the frequency of neurological signs.[6] However, this was random over patient groups and probably did not influence robustness of group comparisons. We hope that our study will draw more attention to the presence of neurological signs in memory clinic patients and make the use of standardized neurological examination more common to facilitate comparison between different centers and diseases. Furthermore, we did not have neuropathological confirmation of our diagnosis and cannot exclude mixed-disease or even misdiagnosis (like concomitant Lewy-body or Parkinson's disease). However, all our patients were carefully screened and diagnosed according current criteria.[8, 10, 22]. Finally, the retrospective cross-sectional study design makes it impossible to draw conclusions on causality.

Unilateral signs were more prevalent in all diagnostic subgroups compared to patients with subjective complaints. Furthermore, we found unilateral signs to be related to WMH in patients with subjective complaints and VaD. A vascular origin of unilateral signs caused by an asymmetric disruption of motor pathways seems plausible. Although mainly related to large vessel disease, the association between unilateral signs and small vessel disease has been shown before in VaD.[9] In MCI and AD, the absence of a relation between WMH and unilateral signs suggests that next to vascular abnormalities other pathological changes might attribute to unilateral signs. Although cortical asymmetry has been found in AD, a possible association with unilateral signs has never been examined.[29, 30] In general, a combination of prominent unilateral signs and focal cortical signs are considered indicative of corticobasal degeneration (CBD) instead of AD.[31] However, a number of case-reports has described patients with unilateral motor signs suspected of CBD, who turned out to have AD at post mortem examination, associated with asymmetric cortical tau burden.[32-35]

Although the concept of vascular parkinsonism is controversial, there seems no doubt that cerebrovascular disease can cause elements of parkinsonism.[36] In non-demented elderly a relation between WMH and extrapyramidal signs has been found.[21] The main hypothesis is that WMH can cause disruption of neural connections between the frontal cortex, thalamus and the striatum resulting in extrapyramidal signs. Remarkably, we found no relation between WMH and extrapyramidal signs in any of the diagnostic groups. However, after adjustment for age and sex only VaD patients showed more extrapyramidal signs compared to patients with subjective complaints, which still seems to imply a vascular etiology. We showed that neurological signs are common in a memory clinic population; the clinical implication of specific neurological signs has to be explored in future studies. Further studies are

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needed to examine the relation between neurological signs and specific atrophy markers. Additionally, with the use of more sophisticated techniques such as diffusion tensor imaging, white matter connectivity of the brain which may be impaired by vascular pathology can be explored. And most important, future research should be aimed at finding the meaning of neurological signs in the different forms of dementia, in terms of prognosis and outcome.

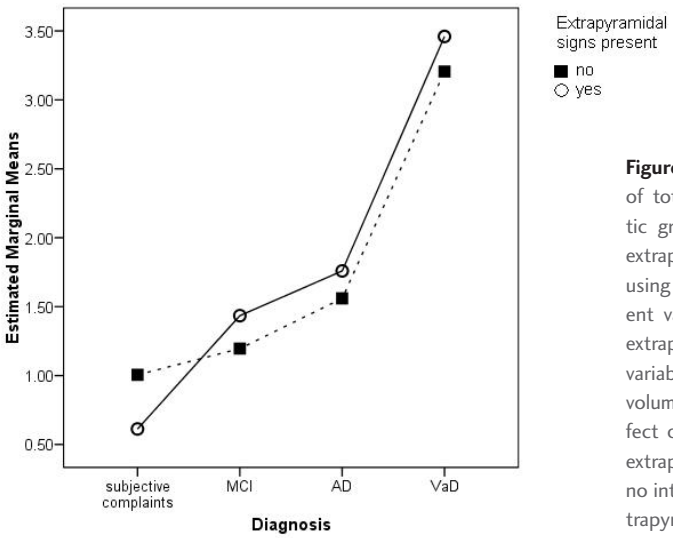

Figure 1; Estimated marginal means of total WMH volumes in the diagnostic groups, categorized by presence of extrapyramidal signs. Two-way ANOVA using total WMH volume as dependent variable, diagnosis and presence of extrapyramidal signs as independent variables, and age, sex and intracranial volume as covariates, showed a main effect of diagnosis ($p<0.001$), but not of extrapyramidal signs ($p=0.62$). There was no interaction between diagnosis and extrapyramidal signs ($p=0.45$).

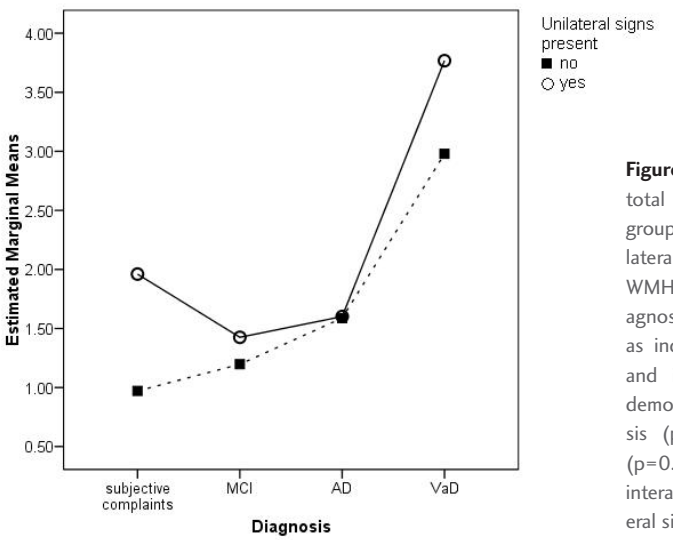

Figure 2; Estimated marginal means of total WMH volumes in the diagnostic groups, categorized by presence of unilateral signs. Two-way ANOVA using total WMH volume as dependent variable, diagnosis and presence of unilateral signs as independent variables, and age, sex and intracranial volume as covariates, demonstrated main effects of diagnosis ($p<0.001$) and of unilateral signs ($p=0.001$). Additionally, there was an interaction between diagnosis and unilateral signs ($p=0.04$).

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4.2 Neurological signs in relation to type of cerebrovascular disease in vascular dementia

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Abstract

Purpose
The aim of this study was to describe the prevalence of a number of neurological signs in a large population of patients with vascular dementia (VaD) and to compare the relative frequency of specific neurological signs dependent on type of cerebrovascular disease.

Methods
706 Patients with VaD (NINDS-AIREN) were included from a large multicenter clinical trial (registration number NCT00099216). At baseline neurological examination, the presence of sixteen neurological signs was assessed. Based on MRI, patients were classified as having large vessel VaD (18%; large territorial or strategical infarcts on MRI), small vessel VaD (74%; white matter hyperintensities (WMH), multiple lacunes, bilateral thalamic lesions on MRI), or a combination of both (8%).

Results
A median number of 4.5 signs per patient was presented (maximum 16). Reflex asymmetry was the most prevalent symptom (49%), hemianopia was most seldom presented (10%). Measures of small vessel disease were associated with an increased prevalence of dysarthria, dysphagia, parkinsonian gait disorder, rigidity and hypokinesia and as well to hemimotor dysfunction. By contrast, in the presence of a cerebral infarct, aphasia, hemianopia, hemimotor dysfunction, hemisensory dysfunction, reflex asymmetry and hemiplegic gait disorder were more often observed.

Conclusion
The specific neurological signs demonstrated by patients with VaD differ according to type of imaged cerebrovascular disease. Even in people who meet restrictive VaD criteria, small vessel disease is often seen with more subtle signs, including extrapyramidal signs, whereas large vessel disease is more often related to lateralized sensorimotor changes and aphasia.

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Introduction

Vascular dementia (VaD) is the second most common type of dementia worldwide.1 At present, the criteria of the National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et al'Enseignement en Neurosciences (NINDS-AIREN) are most often used to diagnose VaD.2 These criteria require the presence of dementia, defined as cognitive decline with interference in activities of daily living, and evidence of cerebrovascular disease. The latter includes both proof on brain imaging and the presence of focal signs on neurological examination. However, little is known about the relative prevalence of specific neurological signs in VaD. The NINDS-AIREN criteria suggest signs such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia and dysarthria.2 Other criteria for VaD requiring focal signs on neurological examination are the Diagnostic and Statistical Manual of Mental Disorders third and fourth edition (DSM III/IV) and the criteria of the International Statistical Classification of Diseases, tenth revision (ICD-10).[3-5] The DSM III and IV mention neurological signs such as exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities or weakness of an extremity. The ICD-10 includes signs such as unilateral increased tendon reflexes, an extensor plantar response or pseudobulbar palsy. Nonetheless, the prevalence of specific neurological signs in VaD patients is not known.

Cerebrovascular disease can be caused by large vessel disease, including large territorial or strategic infarcts, and small vessel disease, consisting of multiple lacunes, white matter hyperintensities (WMH) or bilateral thalamic lesions.[6] It would be plausible that neurological signs differ according to the types of underlying vascular disease. The aim of this study was to investigate the relative prevalence of a number of specific neurological signs in a large population of patients with VaD according to the NINDS-AIREN criteria included in a clinical trial, and to compare neurological signs by type of underlying cerebrovascular disease.

Methods

Study design and patients

Baseline data of 706 patients aged 50-85 years, included in the VantagE study, were used. The VantagE study was a large multicenter, phase III, prospective, randomized, double-blind clinical trial on the effects of rivastigmine in patients with VaD (registration number NCT00099216, Novartis International AG, Basel, Switzerland). Trial inclusion criteria included both fulfilment of the DSM-IV diagnostic criteria for VaD and fulfilment of the NINDS-AIREN criteria for probable VaD, with central assessment of the neuroimaging criteria at the Image Analysis Center (VU Medical Center, Amsterdam, the Netherlands).[2, 4] The NINDS-AIREN criteria for probable VaD were slightly modified:[7] if neuroimaging criteria for subcortical VaD were met as assessed by the central neuroradiologist, patients were not required to have evidence of a temporal relationship between the dementia syndrome and the evidence of cerebrovascular disease. Accordingly, patients with cortical VaD entered the study with a clinical diagnosis of probable VaD, but patients with subcortical VaD were permitted to enter the study with a clinical diagnosis of possible VaD by NINDS-AIREN criteria. Furthermore, focal signs, as evidence of cerebrovascular disease, were expanded to allow presence or history of any findings on neurological examination indicating cerebrovascular disease. Patients had to have a MMSE score of 10-24 to be included in the study. Excluded from entry into the study were patients with a history of stroke within the 3 months prior to baseline unless the patient was considered to have fully stabilized in function; a current diagnosis of any primary neurodegenerative disorder; and a current diagnosis of major depression. Patients with space-occupying lesions or lobar haemorrhages were excluded. All patients gave written informed consent. The study was approved by local Ethics Committees.

Baseline clinical assessment

Diagnostic evaluation included complete medical history, physical and neurological examination, laboratory tests, neuropsychological testing including Mini-Mental State Examination (MMSE)[8] and MRI of the brain. For all patients, a standard neurological exam was performed, during which the presence of sixteen specific neurological signs was assessed: aphasia, dysarthria, dysphagia, pseudobulbar signs (palmomental and snout reflexes), field cut/hemianopia, hemimotor dysfunction indicating upper motor

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neuron lesions, hemisensory dysfunction, reflex asymmetry, babinsky sign, bilateral increased deep tendon reflexes, hemiplegic gait disorder, atactic gait disorder (atactic gait defined as a broad based gait pattern indicative of cerebellar involvement) and parkinsonian type gait disorder, extrapyramidal signs shown by resting or postural tremor, non-spastic rigidity or hypokinesia. All neurological signs were assessed as 'none/absent', 'mild', 'moderate', 'severe' or 'very severe' and as such included, except for the signs hemianopia and reflex abnormalities which were graded as 'none/absent' and 'present'. For this study, all signs were dichotomised as 'none/absent' = 0 and 'present' = 1, and as such used in the data analysis. The following six signs were regarded as 'unilateral signs': aphasia, hemianopia, hemimotor dysfunction, hemisensory dysfunction, reflex asymmetry, hemiplegic gait. Furthermore, we considered 'presence of extrapyramidal signs', determined as presence of one or more of the following: tremor, non-spastic rigidity, hypokinesia or parkinsonian type gait disorder.

MRI protocol

All patients underwent MRI examination before randomization. MRI scanners operating between 0.5 and 1.5 Tesla were used. Axial spin-echo T2-weighted images (T2-WI; echo time [TE]: 80 to 120 ms; repetition time [TR]: 3000 to 4000 ms; slice thickness=5 mm); axial fluid-attenuated inversion recovery (FLAIR) images (TE: 110 to 150 ms; TR: 9000 to 10000 ms; inversion time: 2000 to 2200 ms; slice thickness=5 mm); and axial, sagittal, and coronal spin-echo T1-weighted images (T1-WI; TE: 11 to 20 ms; TR: 500 to 700 ms; slice thickness=5 mm) were acquired.

Image assessment

Vascular abnormalities were evaluated by agreement of two experienced readers blinded to clinical information, with the use of digital image files. The items of the radiological NINDS-AIREN criteria for VaD were determined, according to operational definitions earlier proposed.6 Based on these criteria, patients were classified as having large vessel VaD, small vessel VaD, or a combination of both. For the fulfilment of large vessel disease both a topography and a severity criterion (= lesion of the dominant hemisphere or bilateral hemispheric strokes) has to be met. In case of small vessel disease, for white matter hyperintensities (WMH) both topography and severity criteria have to be met, for multiple lacunae and bilateral thalamic lesions only the topography criterion is sufficient. The degree of WMH severity was rated visually on axial FLAIR and T2-WI images using the Age Related White Matter Changes (ARWMC) scale.[9] In short, WMH are ill-defined hyperintensities of >5mm, rated on a 4-point scale ranging from 0 (no lesions) to 3 (diffuse involvement of the entire region), within 5 regions in each hemisphere. Here, we used the total degree of WMH (range 0-30) by summing the region-specific scores of both hemispheres. Lacunes were rated as presence or absence of multiple lacunes, defined as at least 2 lacunes in the basal ganglia and at least 2 lacunes in the frontal white matter. The presence of bilateral thalamic lesions was assessed, to meet the criterion, at least one lesion in each thalamus had to be present. In addition to assessment of large vessel VaD according to radiological NINDS-AIREN criteria, the presence of a cerebral infarct (of the anterior cerebral artery, in the territory of the posterior cerebral artery, in an association area of the medial cerebral artery or in the watershed area of the carotid territory) was also determined.

Statistical analysis

All statistical analyses were performed using SPSS 14.0 (SPSS Inc). Associations between the number of neurological signs and MMSE score were assessed using partial correlations, controlling for age and sex. For comparison of neurological signs between the different types of VaD (small vessel VaD, large vessel VaD or a combination) chi-square tests were used. Subsequently, to adjust for age and sex, we used logistic regression models with the individual neurological signs as dependent variables, and the different types of VaD as categorical covariate. In addition, associations between neurological signs and specific MRI measures of cerebrovascular disease were assessed using logistic regression analysis, adjusting for age and sex. We used the individual neurological signs as dependent variables. Independent variables were dichotomized as follows: extensive WMH absent (ARWMC < 15) or present (ARWMC ≥ 15) (determined using the median score of the whole population, ARWMC = 15), multiple lacunes and bilateral thalamic lesions absent or present, large vessel infarct - independent of fulfilment of the criteria of large vessel VaD - absent or present. The associations between neurological signs and MRI measures of cerebrovascular disease were tested in separate models.

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Table 1; Patient demographics and characteristics

Number of patients	706
Demographics	
Age (years)	73 (8)
Sex n (%women)	266 (38%)
Education (years)	9 (4)
MMSE	19 (4)
MRI	
Small vessel VaD n(%)	522 (74%)
Large vessel VaD n(%)	126 (18%)
Combination of small and large vessel VaD n(%)	58 (8%)
ARWMC scale*	14.5 (6.2)
Multiple lacunes n(%)	203 (29%)
Bilateral thalamic lesions n(%)	269 (38%)
Cerebral infarct n(%)	226 (32%)

Data are presented as mean(SD) or number(percentage)
* Data missing of 2 patients.

MMSE: mini mental state examination. ARWMC: age related white matter changes. Multiple lacunes: at least 2 lacunes in the basal ganglia and at least 2 lacunes in the frontal white matter. Cerebral infarct: presence of a cerebral infarct independent of fulfilment of criteria of large vessel VaD.

Results

The total study population of 706 VaD patients had a mean (±SD) age of 73±8 years (table 1). On average, patients were mildly-to-moderately demented with a mean MMSE score of 19±4. On the basis of the operational definitions for the radiological part of the NINDS-AIREN criteria, 522 (74%) patients had small vessel VaD, 126 (18%) had large vessel VaD, and 58 (8%) had both small and large vessel VaD. The mean ARWMC score was 14.5±6.2 (median 15). There were 203 (29%) patients who showed multiple lacunes, 269 (38%) patients had bilateral thalamic lesions, and the presence of a cerebral infarct was demonstrated by 226 (32%) patients (n=4 anterior cerebral artery, n=52 posterior cerebral artery, n=57 association area of the medial cerebral artery, n=57 watershed area of the carotid territory, n=56 >1 cerebral infarct).

A median (range) number of 4.5 (0-16) signs per patient were presented (see figure 1; number of presented signs per patient). There were 19 patients who did not present any of the aforementioned selected neurological signs, however, all had shown other neurological signs (e.g. lower facial weakness), or symptoms not otherwise specified. We found a small negative correlation between the number of presented neurological signs and the MMSE (adjusted for age and sex, partial r=-0.14, p<0.001). Prevalence of the sixteen evaluated neurological signs in the total population is shown in figure 2. Reflex asymmetry was the sign which was shown most often (49%), followed by hemimotor dysfunction (44%), dysarthria (43%) and aphasia (41%). The symptom which was most seldom presented was hemianopia (10%).

The relative prevalence of specific neurological signs appeared to be different between patients with small vessel and large vessel VaD (table 2). Dysarthria, dysphagia, parkinsonian type gait disorder and hypokinesia were more prevalent in patients with small vessel VaD compared to patients with large vessel VaD. Patients with large vessel VaD more frequently showed aphasia, hemianopia, hemisensory dysfunction and reflex asymmetry. The results did not change after adjustment for age and sex. Other signs,

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including the babinski sign, atactic gait disorder and tremor, were equally distributed between patients with small vessel or large vessel VaD. In addition, the number of signs presented per patient did not differ between patients with small vessel VaD, large vessel VaD or a combination (p>0.30). In an additional analysis, we compared the presence of at least one unilateral sign (presence of aphasia, hemianopia, hemimotor dysfunction, hemisensory dysfunction, reflex asymmetry or hemiplegic gait) and presence of an extrapyramidal signs (parkinsonian gait, tremor, rigidity or hypokinesia) according to type of cerebrovascular disease. The majority of patients with small vessel VaD (76%) showed at least one unilateral sign, but to a lesser extent (p<0.001) than patients with large vessel VaD, who almost invariably showed unilateral signs (large vessel VaD: 93%; large+small vessel VaD: 90%). Conversely, presence of at least one extrapyramidal sign was highest in patients with small vessel disease (54%), but they were also shown by patients with large vessel disease (large vessel VaD: 41%; large+small vessel VaD: 33%; p=0.001).

Table 2; Prevalence of neurological signs according to type of vascular disease

	Small + vessel VaD (n=522)	Large vessel VaD (n=126)	Small+large vessel VaD (n=58)	Chi-Square Overall, Unadjusted
Aphasia	183 (35)	78 (62)[a]	28 (48)	<0.001
Dysarthria	240 (46)[b,c]	43 (34)	20 (34)	0.02
Dysphagia	114 (22)[b]	16 (13)	8 (14)	0.04
Pseudobulbar signs	155 (30)	37 (29)	14 (24)	0.68
Hemianopia	26 (5)	36 (29)[a]	10 (17)[a]	<0.001
Hemimotor dysfunction	217 (42)	62 (49)	31 (53)	0.09
Hemisensory dysfunction	95 (18)	36 (29)[a]	111 (19)	0.03
Reflexes				
Reflex asymmetry	239 (46)	71 (56)[a]	39 (67)[a]	0.002
Babinski sign	196 (38)	51 (41)	24 (41)	0.74
Bilateral increased deep tendon reflexes	207 (40)	44 (35)	19 (33)	0.41
Gait				
Hemiplegic	118 (23)	34 (27)	21 (36)[a]	0.06
Atactic	150 (29)	39 (31)	14 (24)	0.64
Parkinsonian type	169 (32)[b]	20 (16)	12 (21)	<0.001
Extrapyramidal				
Tremor	74 (14)	16 (13)	4 (7)	0.29
Rigidity	112 (21)	20 (16)	10 (17)	0.32
Hypokinesia	189 (36)[b,c]	34 (27)	13 (22)	0.03

Data given as number (percentage). Comparison of data between the different subgroups was performed first, using chi square test, second, using logistic regression models controlling for age and sex.
Meaning of letters: pair wise group comparison adjusted for age and sex;
a. > patients with small vessel disease; p<0.05
b. > patients with large vessel disease; p<0.05
c. > patients with both small and large vessel disease; p<0.05.

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Table 3; Neurological signs in relation to vascular MRI measurements

	WMH	Multiple lacunes	Bilateral thalamic lesions	Cerebral infarct
Aphasia	0.62 (0.46-0.84)	0.53 (0.37-0.76)	0.56 (0.41-0.77)	1.86 (1.35-2.58)
Dysarthria	1.45 (1.05-1.98)	1.60 (1.13-2.27)	1.28 (0.93-1.76)	0.55 (0.39-0.77)
Dysphagia	1.69 (1.14-2.51)	2.71 (1.81-4.05)	1.56 (1.07-2.89)	0.52 (0.34-0.81)
Pseudobulbar signs	1.28 (0.91-1.79)	1.30 (0.90-1.87)	0.94 (0.67-1.33)	0.83 (0.58-1.18)
Hemianopia	0.34 (0.20-0.57)	0.33 (0.17-0.66)	0.47 (0.27-0.83)	6.63 (3.83-11.48)
Hemimotor dysfunction	0.95 (0.70-1.28)	1.49 (1.06-2.09)	0.94 (0.69-1.29)	1.73 (1.25-2.39)
Hemisensory dysfunction	0.92 (0.63-1.34)	0.84 (0.54-1.29)	0.75 (0.51-1.11)	1.66 (1.13-2.44)
Reflex asymmetry	0.91 (0.67-1.23)	0.85 (0.61-1.20)	0.84 (0.61-1.14)	1.89 (1.37-2.61)
Babinski sign	0.79 (0.58-1.07)	1.12 (0.79-1.58)	1.23 (0.90-1.68)	1.16 (0.84-1.61)
Bilateral increased deep tendon reflexes	1.07 (0.78-1.45)	0.97 (0.68-1.38)	1.22 (0.89-1.67)	0.76 (0.55-1.07)
Hemiplegic gait	1.14 (0.80-1.63)	1.22 (0.83-1.80)	1.38 (0.97-1.96)	1.68 (1.17-2.41)
Atactic gait	1.08 (0.78-1.51)	0.82 (0.56-1.19)	1.04 (0.74-1.45)	0.88 (0.62-1.26)
Parkinsonian type gait	1.45 (1.03-2.03)	2.10 (1.45-3.03)	1.42 (1.01-1.98)	0.44 (0.30-0.66)
Tremor	0.83 (0.53-1.29)	0.99 (0.60-1.63)	0.73 (0.45-1.16)	0.61 (0.37-1.02)
Rigidity	1.53 (1.04-2.25)	1.63 (1.09-2.43)	1.27 (0.87-1.86)	0.68 (0.45-1.04)
Hypokinesia	1.32 (0.95-1.82)	1.41 (0.99-2.00)	1.40 (1.01-1.94)	0.65 (0.46-0.92)

Data given as number (percentage). Comparison of data between the different subgroups was performed first, using chi square test, second, using logistic regression models controlling for age and sex.
Meaning of letters: pair wise group comparison adjusted for age and sex;
a. > patients with small vessel disease; $p<0.05$
b. > patients with large vessel disease; $p<0.05$
c. > patients with both small and large vessel disease; $p<0.05$.

Subsequently we related the various MRI measures of cerebrovascular disease (extensive WMH, multiple lacunes, bilateral thalamic lesions, presence of a cerebral infarct) to the presence of neurological signs (table 3). Extensive WMH was associated with an increased risk of dysarthria, dysphagia, parkinsonian type gait disorder and rigidity. The presence of multiple lacunes additionally showed an increased risk of hemimotor dysfunction. Bilateral thalamic lesions were associated with an increased risk of dysphagia, parkinsonian type gait disorder and hypokinesia. Furthermore, these measures of small vessel disease were associated with a lower risk of aphasia and hemianopia. In contrast, the presence of a cerebral infarct was associated with a higher risk of hemimotor dysfunction, aphasia, hemianopia, hemimotor dysfunction, hemisensory dysfunction, reflex asymmetry and hemiplegic gait disorder, while the risk of dysarthria, dysphagia and extrapyramidal signs was lower in patients with a cerebral infarct.

Discussion

In this large cohort of VaD patients we found that neurological signs of reflex asymmetry (49%), hemimotor dysfunction (44%) and dysarthria (43%) were most prevalent, while hemianopia was rarely observed (10%). Although the number of signs did not differ according to type of underlying cerebrovascular disease, the specific neurological signs differed by type of vascular abnormality.

Overall, little has been reported previously about the relative prevalence of specific neurological signs in VaD.[10-12] Different criteria for VaD suggest different signs (DSM/ICD-10/NINDS-AIREN), and some criteria

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don't require the presence of neurological signs at all (Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC)).[2-5, 13] However, the criterion of presence of focal neurological signs is nowhere clearly specified, neither in the NINDS-AIREN criteria, nor in other criteria of VaD. The NINDS-AIREN criteria only give a suggestion of symptoms that might be encountered. We examined sixteen signs, but there are many other possible signs we did not assess, like the presence of lower facial weakness. On the other hand, our study shows that in addition to signs of lateralization, non-focal signs such as extrapyramidal signs are also often observed in patients with VaD, suggesting that a broad definition of neurological signs should be made. Alternatively, it could be argued that the criterion of neurological signs should be left out of the diagnostic criteria altogether, as with the widespread availability of neuroimaging nowadays, the presence of cerebrovascular disease can be established in a more direct way. In conclusion, these results add to the growing awareness that refinement of the current criteria of VaD may be necessary.

The presence of a cerebral infarct was related to lateralized sensorimotor changes and aphasia, a result one would expect according to the localisation of the infarcts. These signs are the focal signs which are most often mentioned in criteria for VaD, in addition to other signs such as the babinski sign and pseudobulbar signs, which were equally prevalent among patients with cerebral infarcts and small vessel disease. In contrast to large vessel infarcts which are likely to produce acute signs, the onset of small vessel VaD is often insidious and more subtle neurological signs would be expected. The associations we found between small vessel disease and subtle signs of dysphasia and dysarthria are in agreement with previous findings.[11, 14] Furthermore, we found associations between small vessel disease, including WMH, lacunes and bilateral thalamic lesions, and extrapyramidal signs such as rigidity, hypokinesia and parkinsonian gait disturbance. In literature the concept of vascular parkinsonism is controversial, but associations between small vessel disease and extrapyramidal signs have been reported before.[15, 16] Nonetheless, none of the criteria for VaD suggests the presence of extrapyramidal signs as a qualifying neurological sign. Gait disorders are common in VaD, and in the NINDS-AIREN criteria specified as clinical feature consistent with the diagnosis.[2] In small vessel disease, gait disturbances have traditionally been classified as 'marche à petit pas', an apraxic-atactic or Parkinsonian gait.[14] We demonstrated a difference in gait pattern between small vessel and large vessel VaD patients, with a hemiplegic type gait disturbance in large vessel disease and parkinsonian type gait disturbance in small vessel disease.

Strengths of the present study include the large study population, as it is one of the largest clinical series of patients affected by VaD to date. Additionally, the screening for fulfilment of radiological criteria for probable VaD was performed carefully by central assessment. To diagnose patients with VaD the NINDS-AIREN criteria were used, widely used and generally considered accurate criteria, although the criteria have been shown not to be interchangeable with other diagnostic methods for VaD.[10] A limitation includes the study design of a cross-sectional cohort study, which precludes the assessment of causality or the evolution of symptomatology. Another limitation is possible inter-rater variability due to the performance of neurological examination in several centres by several assessors. Ideally, reliability data should have been provided, but for the present study, these were not available. Furthermore, setting, entry criteria and other design features of a randomized clinical trial may have introduced a selection bias on the inclusion of patients.

Finally, the unavoidable circularity of studying neurological signs in VaD patients – that by definition are required to have neurological signs – is a complex issue. However, we feel that the description of the

relative frequency of a large number of specific neurological signs indeed adds to the field. Moreover, we showed that specific signs were related to specific types of imaged vascular damage. Further studies should endeavour to avoid this inherent circularity, for example by studying presence of neurological signs in relation to MRI abnormalities in a broader group of patients with dementia, irrespective of the specific nosological diagnosis.

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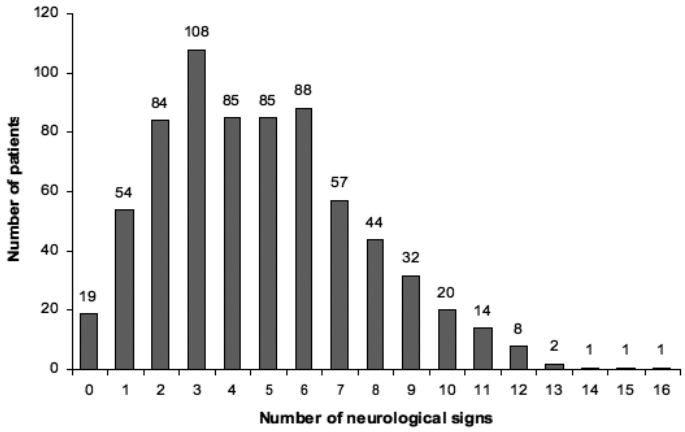

Figure 1; Number of neurological signs presented per patient.
Frequency distribution of the number of neurological signs per patient of the total population (n=706). 19 Patients did not present any of the sixteen neurological signs under study, however, all had shown at least one other neurological sign.

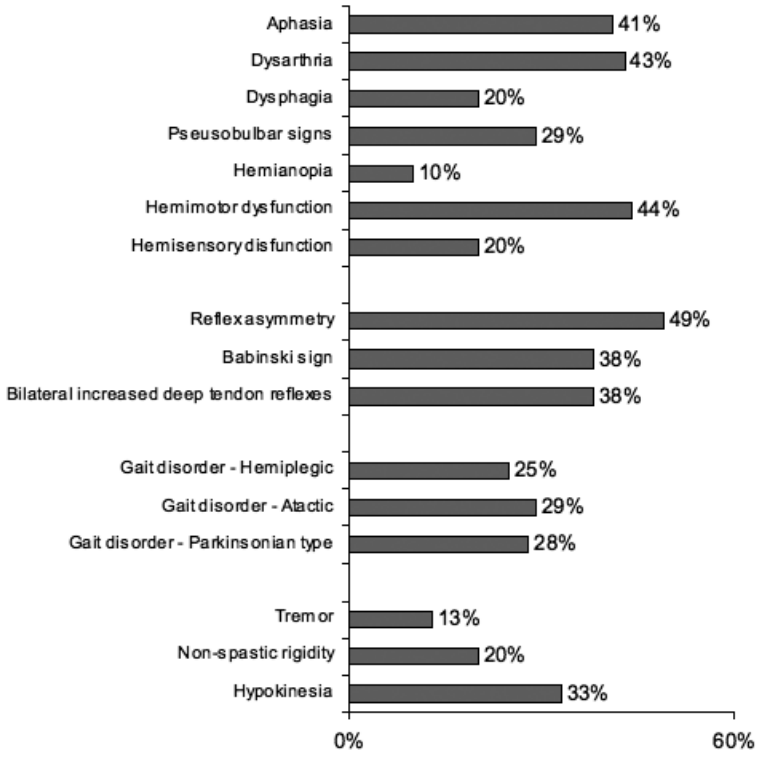

Figure 2; Prevalence of neurological signs.
Percentage of patients of the total population presenting individual neurological signs. All neurological signs were rated in n=706 patients, except for hemianopia which had 2 missing values (n=704).

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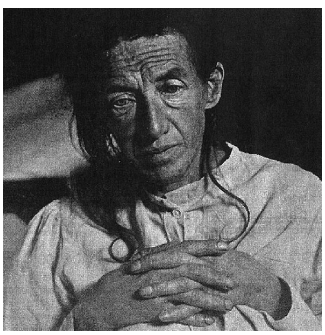
Part 5

Neuropsychiatric symptoms in Alzheimer's disease and vascular dementia; associations with MRI measures



Picture of Auguste D.,

the patient described by Alois Alzheimer who would have

suffered next to amnesia and disorientation, from depression,

hallucinations and jealousy towards her husband.

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5.1 Behavioural and psychological symptoms are not related to WMH and MTA in AD

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Abstract

Background

The neuropathology of behavioural and psychological symptoms is much less understood than xthe neuropathology of cognitive impairment in AD. On MRI, medial temporal lobe atrophy (MTA) is presumed to reflect Alzheimer-type pathology. White matter hyperintensities (WMH) are considered markers of vascular pathology.
Aim: We investigated differences in prevalence of behavioural and psychological symptoms in AD according to the presence of MTA and WMH on MRI.

Methods

Behavioural and psychological symptoms of 111 consecutive AD patients were assessed using the Neuropsychatric Inventory (NPI). Symptoms were considered present when the score was ≥1. On MRI, MTA was rated using the 5-point Scheltens-scale and WMH using the 4-point Fazekas-scale. Both MRI measures were dichotomised (MTA: absent 0/1, present 2-4; WMH absent 0/1, present 2/3).

Results

Of the 111 AD patients, 60(55%) had MTA, and 32(29%) had WMH. The presence of MTA was associated with the presence of WMH (2=11.8, p<0.001). The prevalence of behavioural and psychological symptoms – defined as a NPI score of ≥1 on at least one symptom – was 74%. The median NPI score of the total study population was 6(0-41). There was no difference in prevalence according to MTA (p=0.53) or WMH (p=0.18). On inspection of individual NPI items, neither MTA, nor WMH was related to any of the symptoms.

Conclusions

There were no differences in prevalence of behavioural and psychological symptoms according to MTA or WMH, as rated on MRI. This suggests that the occurrence of those symptoms depends on other determinants, such as coping style or genetic make-up.

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Introduction

Alzheimer's disease (AD) is the most common form of dementia, characterized by gradually increasing cognitive impairment.[1] In addition to cognitive impairment, behavioural and psychological symptoms in AD are considered to be equally important.[2] These symptoms have been shown to be associated with worse prognosis, higher cost of care, earlier institutionalisation and increased caregiver burden.[3, 4] However, little is known about the radiological underpinnings of these behavioural and psychological symptoms.

On MRI, medial temporal lobe atrophy (MTA) and white matter hyperintensities (WMH) are both commonly observed in AD. MTA is presumed to reflect disease severity as it has been related to the burden of Alzheimer-type pathology.[5, 6] WMH are regarded as suggestive of vascular pathology and considered to reflect ischemic damage to the brain.[7] MTA and WMH are both associated with cognitive problems in AD.[8, 9] Moreover, both MRI abnormalities have been shown to be involved in the earliest stages of cognitive decline, even before dementia.[10] In AD, MTA especially has been related to memory impairment, whereas WMH has been reported to affect frontal lobe function resulting in executive dysfunction.[11, 12] Still, it is unclear whether MTA and WMH are also associated with other symptoms in dementia such as behavioural and psychological symptoms. Hypothetically these may be caused by disruption of the connections between the anterior cingulated gyrus and other cortical and subcortical area's or by affecting structures relevant to emotion and social behaviour including the amygdala and anterior temporal cortex.

Few studies have focused on behavioural and psychological symptoms and MRI abnormalities in AD. Only one previous study examined involvement of the medial temporal lobe and showed an association with delusions in a small group of AD patients.[13] Reports about the role of WMH and behavioural and psychological symptoms in AD have been conflicting. Associations between WMH and apathy,[14] depression,[15] suicidal ideation,[16] delusional misidentification [17] and aberrant motor behaviour [18] have been described. However, the studies were relatively small, and none of the studies could confirm the results of the previous reports. Moreover, other studies did not find any relation between WMH and psychiatric symptoms.[19-21] We hypothesized that, since MTA is known to progress along with dementia severity, the presence of MTA would be related to the occurrence of behavioural and psychological symptoms. Furthermore we expected vascular involvement as illustrated by WMH to express with a different behavioural and psychological profile compared to patients without vascular involvement. WMH in non-demented older subjects have been associated with depressive symptoms,[22] and we hypothesized that likewise, affective symptoms would be promoted by WMH in AD patients as well.

To our knowledge, no previous report has examined both MRI markers in relation to behavioural and psychological symptoms in dementia. We have therefore assessed the associations between these symptoms and MTA and WMH in a relatively large sample of AD patients attending a memory clinic.

Methods

We consecutively recruited 111 patients with probable AD from the outpatient memory clinic of the Alzheimer Centre of the VU University Medical Centre (VUmc). Standardized dementia assessment included medical history, neurological exam, laboratory tests, neuropsychological testing including Mini-Mental State Examination (MMSE),[23] electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain. Diagnoses were made in a multidisciplinary consensus meeting according to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) diagnostic criteria.[1] The study was approved by the local Medical Ethical Committee. All patients gave written informed consent.

Behavioural and psychological assessment

To evaluate behavioural and psychological symptoms (including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability, and aberrant motor behaviour), the Neuropsychiatric Inventory (NPI 10-item), an informant rated

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instrument, was used.[24] For each neuropsychiatric domain, frequency (range 0 – 4) and severity (range 0 – 3) are rated. Subsequently, the domain score is calculated as the product of the frequency and severity. The sum of the 10 domain scores provides the total NPI score (maximum score =120). Presence of behavioural and psychological symptoms was defined as a score of 1. The abbreviated Geriatric Depression Scale (GDS-15) was used to additionally assess depressive symptoms.[25]

MRI

MRI was performed on a 1.0 Tesla machine (Magnetom Impact Expert Siemens AG, Erlangen, Germany) following a standard protocol, including coronal T1-weighted 3D MPRAGE (magnetization prepared rapid acquisition gradient echo; 168 slices, FOV 250mm, matrix 256x256, slice thickness 1.5 mm, TE: 7ms, TR: 15 ms, TI 300 ms, flip angle 15 degrees) and axial FLAIR (fluid attenuated inversion recovery, 17 slices, FOV 250mm, matrix 256x256, slice thickness: 5mm, interslice gap: 1.5mm, TE: 105ms, TR: 9000ms, TI 2200 ms, flip angle 180 degrees). Visual rating of MTA was performed on coronal T1-weighted images according to the 5-point (0-4) Scheltens scale.8 The degree of WMH severity was rated visually on axial FLAIR images using the 4-point (0-3) Fazekas scale.26 Both MRI measures were dichotomised (MTA average score 0/1 = no atrophy, MTA score 2–4 = atrophy; WMH grade 0/1 = no WMH, grade 2/3 = WMH present).

Statistical analysis

Statistical analysis was performed by means of SPSS 12.0 (SPSS Inc). Group comparisons were performed using chi-squared tests for dichotomous outcome variables and independent samples t-tests for continuous data. Subsequently, we used logistic regression models with the individual NPI symptoms as dependent variables, and the presence of MTA or WMH as categorical covariate, adjusting for age, sex and MMSE.

Table 1; Characteristics of patients

N	111
Sex (% female)	62 (57%)
Age	70 (9)
Mini Mental State Examinationa	20 (5)
Geriatric Depression Scaleb	2.5 (0 – 9)
Neuropsychiatric Inventory (% ≥ 1)	81 (74%)
NPI score	6 (0 – 41)
Medial Temporal lobe Atrophy present	60 (55%)
MTA score	1.5 (0 – 4)
White Matter Hyperintensities present	32 (29%)
WMH score	1 (0 – 3)

Data are represented as mean (standard deviation), median (range) or n (percentage).
NPI = neuropsychiatric inventory, MTA = medial temporal lobe atrophy (present = Scheltens score ≥2), WMH = white matter hyperintensities (present = Fazekas score 2/3).
a. data available for 105 patients.
b. data available for 102 patients.

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Results

Demographic, clinical and MRI variables are shown in table 1. More than half of the patients had MTA, while one third of patients showed moderate or severe WMH. The combination of both MTA and WMH was observed in 26 (23%) of the patients. The presence of MTA was associated with the presence of WMH (χ^2=11.8, p=0.001). Both MTA and WMH were associated with a higher age (MTA t=4.3, p=0.03; WMH t=4.3, p<0.001). Patients with MTA tended to have a lower MMSE (t=2.1, p=0.057), but there was no relation between WMH and MMSE (t=0.2, p=0.22). There were no differences in sex or depressive symptoms as measured using the GDS according to MTA or WMH.

In the total cohort of 111 patients, the prevalence of any behavioural or psychological symptom was 74%, with a median NPI score of 6 (range 0 – 41). Apathy and irritability were the most common symptoms in the whole group, euphoria was the rarest symptom (affecting 60%, 26% and 0% patients, respectively). The presence of any symptom was related to a higher GDS score (t=4.2, p<0.001), and related to a lower MMSE (t=2.5, p=0.01). There was no difference in prevalence of any behavioural or psychological symptom according to MTA (χ^2=0.4, p=0.53) or WMH (χ^2=1.8, p=0.18). Also the combination of MTA and WMH showed no difference in presence of symptoms compared to patients without MTA or WMH (χ^2=0.2, p=0.64). Figures 1 and 2 show the prevalence of individual behavioural and psychological symptoms according to the presence of MTA and WMH, respectively. We did not find a relation between MTA or WMH and any of the individual symptoms (all p>0.12). These results remained unchanged after adjustment for age, sex and MMSE.

Discussion

The main finding of this study is the absence of any association between the behavioural and psychological profile and MTA or WMH, two widely used MRI markers in AD. On examination of individual NPI items, neither MTA nor WMH was related to any of the symptoms. These findings suggest that the presence of behavioural and psychological symptoms depends on other determinants.

We hypothesized that MTA would be related to the prevalence of symptoms. However, we did not find an association between any behavioural or psychological symptom and MTA. Our findings are in agreement with the observation that – unlike cognition that gradually declines in the course of the disease – behavioural and psychological symptoms may have a more fluctuating manifestation.[27] Apparently behavioural and psychological symptoms are not directly related to disease progression as measured using MTA, but depend on other factors. A previous report examined AD patients with delusions, and showed asymmetric involvement of the medial temporal lobe.[13] However, a different study method was used; only delusional symptoms were examined, while we evaluated the whole spectrum of behavioural and psychological symptoms, and CT-scans were used instead of MRI. To our knowledge, other behavioural or psychological symptoms have never been explored in relation to MTA in AD patients. In non-demented patients, smaller hippocampal volume has been related to depression.[28, 29] As possible cause of this decline in volume in depressed patients, repeated stress and associated glucocorticoid excess have been suggested.[28] On the contrary, decrease of hippocampal volume in AD has been related to the extent of Alzheimer-type neuropathology.[5] Probably, primary depression should be considered as a psychiatric illness which develops following a different mechanism than behavioural and psychological symptoms in AD.

We hypothesized that vascular involvement as indicated by WMH would express with a different clinical presentation of behavioural and psychological symptoms compared to patients without vascular involvement, but we could not objectify such dissimilarity. The concept of 'vascular depression' assumes that a disruption of fronto-striatal circuits, due to vascular lesions such as WMH, predisposes, perpetuates or exacerbates depressive symptoms.[30] We were not able to show any difference in prevalence of neuropsychological or behavioural symptoms in AD patients with or without vascular involvement, measured as WMH. However, others did find a relation in AD patients. Associations between WMH and apathy,[14] depression,[15] suicidal ideation,[16] delusional misidentification[17] and aberrant motor behaviour[18] have been described. Nevertheless, none of the studies could confirm the results of the

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previous reports and other reports were negative.[19-21] Moreover, a recent study showed that patients with AD and with vascular dementia have similar neuropsychiatric profiles.[31] This provides further support for our results, that within a group of AD patients, additional vascular involvement does not influence the behavioural and psychological profile.

Among the strengths of our study is the relatively large study population, compared to previous reports. In addition, we simultaneously examined both MTA and WMH, two widely used MRI markers of pathology in AD, in relation to a wide spectrum of psychiatric domains using the NPI. The use of the NPI may also imply a limitation of the study. Information of the caregiver is used to grade the occurrence and severity of neuropsychiatric symptoms in patients. The results therefore may partially reflect coping style of the caregiver. To measure MTA and WMH we used rather crude measurements, which on the other hand are widely used and easily applicable in clinical practice. Possibly, however, more sophisticated and quantitative measures may reveal correlations that we were not able to detect. Some authors have proposed regional associations between brain changes an behavioural and psychological symptoms.[14, 32] In further study work it would be interesting to explore whether there was a relationship between behavioural and psychological symptoms and regional WMH or atrophy of specific brain regions, such as the amygdala or certain cortical (e.g. frontal) areas. Furthermore, the general burden of neuropsychiatric symptoms (median NPI score 6) in our cohort was quite low. It would be important in future studies also to investigate subjects with higher burden of symptoms, as it is possible that associations may then be seen. Nonetheless, we feel that our results suggest that the occurrence of behavioural and psychological symptoms in AD patients is at least partly dependent on other determinants, such as caregiver characteristics or genetic factors[33, 34]

In conclusion, we showed that behavioural and psychological symptoms do have a high prevalence among AD patients, which emphasizes the importance to recognize these symptoms, especially with regard to care and prognosis. However, we were not able to identify a relation between behavioural and psychological symptoms and visual rating of MTA and WMH on MRI. Further research in this field, using more sophisticated measures, is necessary.

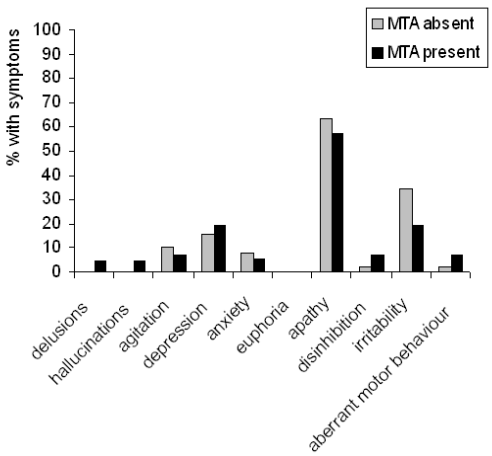

Figure 1; Prevalence of behavioural and psychological symptoms according to presence of MTA. A symptom was considered present with a NPI score of ≥1. MTA was considered present with a Scheltens score of ≥2.

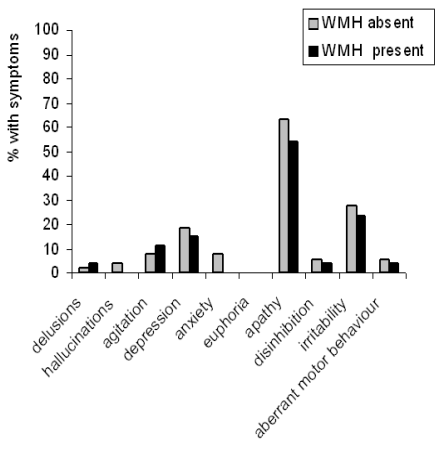

Figure 2; Prevalence of behavioural and psychological symptoms according to presence of WMH. A symptom was considered present with a NPI score of ≥1. WMH was considered present with a Fazekas score of 2/3

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5.2 Behavioural and psychological symptoms in vascular dementia; differences between small vessel and large vessel disease

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Abstract

Aim

We investigated the prevalence of behavioural and psychological symptoms in vascular dementia (VaD) from baseline data of the VantagE study and compared the severity and relative frequency of symptoms between small vessel VaD and large vessel VaD.

Methods

Behavioural and psychological symptoms of 484 VaD patients included in a large multicenter clinical trial (registration number NCT00099216) were determined using the 12-item Neuropsychiatric Inventory (NPI). Symptoms were considered present when the score was ≥1. Based on MRI, patients were classified as having small vessel VaD (83%) or large vessel VaD (17%).

Results

Behavioural and psychological symptoms were reported in 92% of the VaD patients. The median NPI score of the total study population was 9 (0-76), with a median number of 3 symptoms per patient. Apathy (65%) was most prevalent, followed by depressive symptoms (45%), irritability (42%) and agitation/aggression (40%). Patients with small vessel VaD reported more apathy, aberrant motor behaviour and hallucinations than patients with large vessel VaD ($p<0.05$). In contrast, patients with large vessel VaD reported a higher severity of agitation/aggression and euphoria ($p<0.05$).

Conclusion

Behavioural and psychological symptoms are common in VaD. Patients with small vessel and large vessel VaD demonstrate different profiles of symptoms, with especially more apathy in small vessel VaD and more agitation/agression in large vessel VaD.

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Introduction

Behavioural and psychological symptoms are increasingly recognized as important clinical features of the dementia syndrome. These symptoms impact on the quality of life of patients with dementia, and have been associated with increased caregiver burden, more rapid progression of cognitive and functional decline, earlier institutionalization and mortality.[1] In Alzheimer's disease (AD), a prevalence of about 90% for behavioural and psychological symptoms has been reported.[2, 3] Vascular dementia (VaD) is the second most common type of dementia worldwide, but in contrast to AD, only a couple of small studies on behavioural and psychological symptoms have been conducted in VaD patients.

In spite of the modest body of literature, diagnostic criteria for VaD such as the criteria of the National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et al'Enseignement en Neurosciences (NINDS-AIREN), specify that clinical features consistent with the diagnosis include personality and mood changes, abulia, depression and emotional incontinence.[4] Results of studies on behavioural and psychological symptoms in VaD differ slightly, but apathy, depressive symptoms and agitation/aggression have been reported as symptoms of highest prevalence and severity.[5-10] These former studies are hampered by methodological shortcomings, as VaD was mostly not the main diagnosis under study as studies investigated a large sample of AD patients with a small additional group of VaD patients. Furthermore, due to differences in research populations, diagnostic criteria, and methods to assess presence of symptoms, results are difficult to compare.
According to the NINDS-AIREN criteria for VaD, neuroimaging is required to demonstrate cerebrovascular disease. VaD can be based on small vessel disease (lacunes, white matter hyperintensities or bilateral thalamic lesions) or large vessel disease (large territorial or strategic infarcts). We hypothesized that the behavioural and psychological profile of VaD patients differs according to type of underlying vascular disease. In small vessel VaD symptoms such as apathy would be expected due to disruption of corticosubcortical circuits, while in large vessel VaD a wide range of symptoms would be plausible, related to size, location and cortical involvement of the large vessel infarct. For example after ischemic stroke a broad variety of psychological and behavioural symptoms has been demonstrated with depressive symptoms and irritability being of highest frequency.[11] In VaD, only two previous reports made the differentiation between small vessel and large vessel disease.[6, 9] Both studies used computed tomography with different criteria to define small vessel and large vessel VaD, and inconsistent results were reported.

The aim of this study was to determine the presence of behavioural and psychological symptoms in a large cohort of 484 VaD patients enrolled in a clinical trial, and to compare the severity and prevalence of symptoms according to type of underlying vascular disease (small vessel or large vessel) as assessed on magnetic resonance imaging (MRI) using well-defined radiological criteria.[12]

Methods

Study design and patients

We examined the baseline data of patients enrolled into the VantagE study (registration number NCT00099216). The VantagE study was a multicenter, phase III, prospective, randomized, double-blind, placebo-controlled clinical trial of the effects of rivastigmine in patients with mild to moderate VaD.[13] Trial inclusion criteria included both fulfilment of the DSM-IV diagnostic criteria for VaD and fulfilment of the NINDS-AIREN criteria for VaD according to central assessment of the neuroimaging criteria.[4] The NINDS-AIREN criteria for probable VaD were slightly modified: if neuroimaging criteria for subcortical VaD were met as assessed by the central neuroradiologist, patients were not required to have evidence of a temporal relationship between the dementia syndrome and the evidence of cerebrovascular disease. Accordingly, patients with cortical VaD entered the study with a clinical diagnosis of probable VaD, but patients with subcortical VaD were permitted to enter the study with a clinical diagnosis of possible VaD by NINDS-AIREN criteria. Excluded from entry in the study were patients with a current diagnosis of any primary neurodegenerative disorder, a current diagnosis of major depression, or a history of stroke within the 3 months before baseline unless the patient was considered to have fully stabilized in function. Patients with space occupying lesions or lobar hemorrhages were excluded. For the current

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study, patients were required to have data on psychological and behavioural symptoms and MRI data (n=525). Furthermore, MRI data had to be classifiable as either fulfilment of criteria of small vessel VaD or fulfilment of criteria of large vessel VaD (see below; n=484). Patients who fulfilled criteria for both small vessel and large vessel disease were excluded (n=39). All patients gave written informed consent. The study was approved by the local Ethics Committees.

Baseline clinical assessment

Diagnostic evaluation included complete medical history, physical and neurological examination, laboratory tests, neuropsychological testing including Mini-Mental State Examination (MMSE), and MRI of the brain. The use of sleep medication (yes/no), antidepressants (yes/no) and other behavioural regulating medication (including antipsychotics and anxiolytics; yes/no) was recorded. Global staging of dementia severity was performed with the Global Deterioration Scale (GDS). To evaluate behavioural and psychological symptoms (including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night time behaviour disturbances and appetite changes), the Neuropsychiatric Inventory (NPI, 12-item), an informant rated instrument, was used.[14] Using the NPI, the twelve behavioural domains are evaluated by sample questions such as: delusions (Does the patient believe that others are stealing from him?); hallucinations (Does the patient talk to people who are not there?); agitation/aggression (Is the patient uncooperative, resistive to help from others?); depression/dysphoria (Does the patient say or act that he is sad or in low spirits?) anxiety (Does the patient say that he is worried about planned events?); euphoria (Does the patient find humour in and laugh at things that others do not find funny?); apathy (Does the patient seem less spontaneous and less active than usual?); disinhibition (Does the patient say crude things or make sexual remarks that he would not usually say?); irritability (Does the patient have sudden flashes of anger?); aberrant motor behaviour (Does the patient pace around the house without apparent purpose?); night time behaviour disturbances (Does the patient have problems with sleeping and is he often awake during the night?); appetite changes (Has the patient changed in appetite, eating habits or in physical weight?). For each neuropsychiatric domain, severity (0=absent, 1=mild, 2=moderate, 3=severe) and frequency (0=absent, 1=occasionally, less than once per week, 2=often, about once per week, 3=frequently, several times per week but less than every day, 4=very frequently, once or more per day or continuously) are rated. Subsequently, the domain score is calculated as the product of the frequency and severity. The sum of the 12 domain scores provides the total NPI score (maximum score = 144). Presence of behavioural and psychological symptoms was defined as a score of ≥ 1.

MRI protocol

All patients underwent MRI examination before randomization. Scanners operating between 0.5 and 1.5 Tesla were used. Axial spin-echo T2-weighted images (T2-WI; echo time [TE]: 80 to 120 ms; repetition time [TR]: 3000 to 4000 ms; slice thickness=5 mm); axial fluid-attenuated inversion recovery (FLAIR) images (TE: 110 to 150 ms; TR: 9000 to 10000 ms; inversion time: 2000 to 2200 ms; slice thickness=5 mm); and axial, sagittal, and coronal spin-echo T1-weighted images (T1-WI; TE: 11 to 20 ms; TR: 500 to 700 ms; slice thickness=5 mm) were acquired.

Image assessment

Image assessment was performed centrally at the Image Analysis Center (VU Medical Center, Amsterdam, the Netherlands) by agreement of two experienced readers blinded to clinical information, with the use of digital image files. The assessment of vascular abnormalities included the items of the radiological NINDS-AIREN criteria for VaD, according to operational definitions earlier proposed.[12] Based on these criteria, patients were classified as having large vessel VaD (strategic large vessel infarct of the dominant hemisphere or bilateral hemispheric strokes) or small vessel VaD (white matter hyperintensities involving at least of the white matter, multiple lacunes or bilateral thalamic lesions).

Statistics

Statistical analysis was performed by means of SPSS 14.0 (SPSS Inc). To compare baseline characteristics between small vessel and large vessel VaD chi-squared tests were used for dichotomous variables, Mann-Whitney U tests for non-parametric data and independent sample t-tests for continuous data.

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Comparison of the total NPI score, the total number of symptoms and the NPI score per symptom between small vessel VaD and large vessel VaD was performed using Mann-Whitney U tests. The prevalence of symptoms (present/not present) was compared between large vessel and small vessel VaD using chi-squared test. Subsequently, to control for age, sex, MMSE, dementia duration and the use of psychotropic medication, logistic regression analysis was performed with the individual NPI symptoms as dependent variable, and the different types of VaD (small vessel or large vessel) as independent variable.

Table 1; Patient demographics and characteristics

	Small vessel VaD	Large vessel VaD	p value
Number of patients (%)	401 (83%)	83 (17%)	
Demographics			
Age (years)	73 (8)	71 (9)	<0.05
Sex n (%women)	154 (38%)	28 (34%)	ns
Education (years)	9 (4)	11 (4)	<0.05
Duration of dementia (years)	2(2)	3 (3)	<0.05
Medication – sleep disorder n(%)	47 (12%)	7 (9%)	ns
Medication – antidepressant n(%)	94 (24%)	19 (23%)	ns
Medication – behavioural disorder n(%)	47 (12%)	5 (6%)	ns
MMSE	19 (4)	19 (4)	ns
GDS	4 (2-6)	4 (2-5)	ns
Neuropsychiatric Inventory % ≥1	372 (93%)	75 (90%)	ns
Total NPI score	9 (0-76)	9 (0-45)	ns

Data are presented as mean(SD), median(range) or number(percentage). Comparison of data between small vessel VaD and large vessel VaD was performed using chi-squared tests, Mann-Whitney U tests or independent sample t-tests when appropriate.
MMSE: mini mental state examination. GDS: global deterioration scale
NPI: neuropsychiatric inventory.

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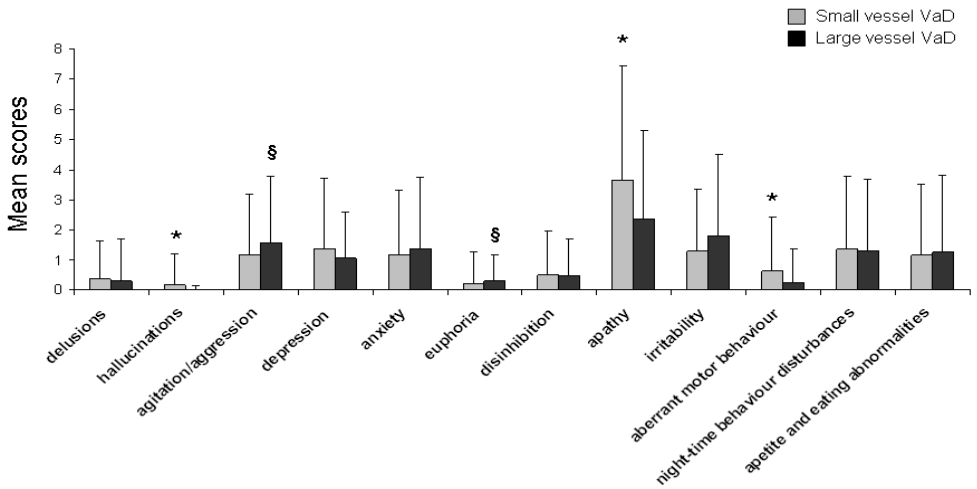

Figure 1; Severity of NPI symptoms in small vessel VaD and large vessel VaD.
Mean scores of individual behavioural and psychological symptoms in patients with small vessel VaD (n=401) and large vessel VaD (n=83). Please note that, although means (with standard deviations) are represented in the figure, statistics were performed using Mann-Whitney U tests.
* higher in small vessel VaD $p<0.05$;
§ higher in large vessel VaD $p<0.05$.

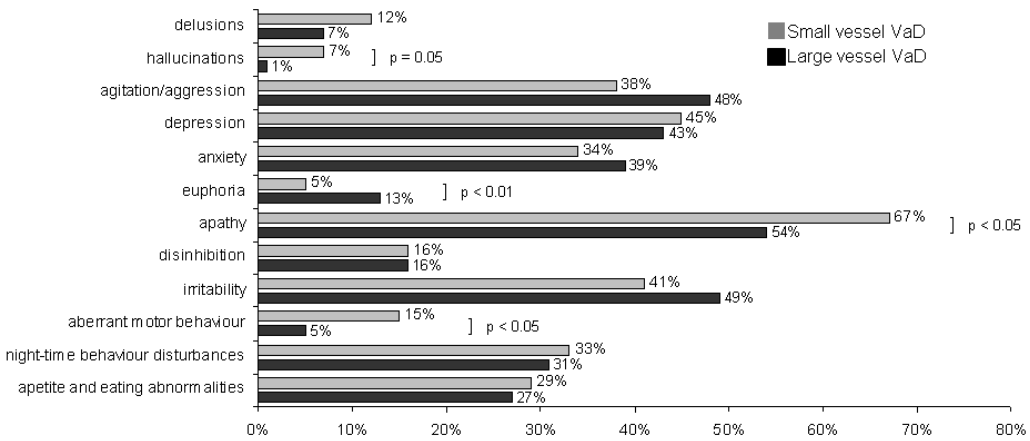

Figure 2; Prevalence of NPI symptoms in small vessel VaD and large vessel VaD.
Prevalence of individual psychological and behavioural symptoms in patients with small vessel VaD (n=401) and large vessel VaD (n=83). A symptom was considered present with a NPI score ≥1. Comparison of data was performed using chi-squared tests.

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Results

Baseline demographics are shown in table 1. The total population included n=484 VaD patients with a mean(SD) age of 72(8) yrs and included 182(38%) women. On average, patients were mildly-to-moderately demented with a mean MMSE score of 19(4) and a median(range) GDS score of 4(2-6). Based on the operational definitions for the radiological part of the NINDS-AIREN criteria, n=401(83%) had small vessel VaD and n=83(17%) had large vessel VaD. Patients with small vessel VaD were slightly older but had a shorter duration of dementia compared to patients with large vessel VaD. The percentage of patients using psychotropic medication was comparable in both groups.

In the total cohort, the prevalence of any behavioural or psychological symptom was 92%, with a median NPI score of 9(0-76). A median number of 3(0-11) symptoms per patient was reported. Thirty-seven patients did not report any symptom, and two patients reported 11 of the 12 NPI symptoms. Apathy was the symptom that was reported most often (65% of the total population), followed by depressive symptoms (45%), irritability (42%) and agitation/aggression (40%). Hallucinations (6%) and euphoria (6%) were the symptoms that were reported most infrequently.

No differences were found between small and large vessel VaD comparing the total NPI score and the total number of reported symptoms per patient. However, there appeared to be differences in the individual NPI symptoms between small vessel VaD and large vessel VaD (figure 1). Patients with small vessel VaD had a higher severity of apathy, aberrant motor behaviour and hallucinations than patients with large vessel VaD. In contrast, symptoms of agitation/aggression and euphoria were more severe in large vessel VaD compared to small vessel VaD. The prevalence of individual NPI symptoms in small vessel and large vessel VaD was comparable (figure 2). Patients with small vessel VaD had a numerically higher prevalence of apathy, aberrant motor behaviour and hallucinations than patients with large vessel VaD. Patients with large vessel VaD were reported as having more frequent euphoria compared to patients with small vessel VaD. Furthermore, the prevalence of agitation/aggression (48% compared to 38%) and irritability (49% compared to 41%) was higher in large vessel than small vessel VaD, but these differences did not reach significance. Logistic regression analysis with adjustment for age, sex, MMSE, dementia duration and the use of sleep-, antidepressant- and behavioural-medication, yielded comparable results, with a significantly higher risk of apathy and aberrant motor behaviour for small vessel VaD than large vessel VaD, and more euphoria in large vessel VaD (all $p<0.05$).

Discussion

The main finding of the present study is that the profile of neuropsychiatric symptoms differs between small vessel and large vessel VaD. Apathy, aberrant motor behaviour and hallucinations are more severe and more prevalent in patients with small vessel VaD compared to large vessel VaD. Conversely, agitation/aggression and euphoria are more severe in patients with large vessel VaD.

The observed prevalence of 92% of any behavioural and psychological symptom in the total study population is in agreement with earlier reports.[5, 8, 10, 15] Furthermore, the highest prevalence for apathy, followed by depressive symptoms, irritability and agitation/aggression confirms previous findings in populations of VaD patients.[5, 6] Other studies have demonstrated a slightly different order of these symptoms, for example with the highest frequency of depressive symptoms, followed by agitation/aggression and apathy.[8, 10] In our study, apathy had the greatest severity and prevalence in both small vessel and large vessel VaD. Both severity and prevalence were even significantly higher in small vessel VaD than in large vessel VaD. Apathy may be induced by changes in the neural networks that generate and control goal directed actions, that are mostly represented within the prefrontal cortex connections to basal ganglia, thalamus, and limbic system structures.[16] It seems plausible that disruption of the white matter tracts between frontal cortex and basal ganglia by severe WMH may result in apathy. Furthermore, other vascular damage according to the definition of small vessel disease include multiple lacunes (at least 2 lacunes in the frontal lobe and 2 lacunes in the basal ganglia) or bilateral thalamic lesions, also structures that are thought to play a role in the origin of apathy.[12, 16] In line with our results, a recent study in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) demonstrated that CADASIL patients with apathy had a

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higher WMH burden and more lacunes compared to patients without apathy.[17] Furthermore, apathy has been recognized as important clinical feature in many neurodegenerative diseases, like Alzheimer's disease, Parkinson's disease and supranuclear palsy.[18-20] We have no neuropathological confirmation of the diagnosis of VaD and the possibility of concomitant pathology or even misdiagnoses cannot be excluded. However, all our patients were carefully diagnosed by the clinical and radiological NINDS-AIREN criteria, which are known to have a high specificity[21]

Patients with large vessel VaD showed a different profile of neuropsychiatric symptoms, with a higher severity of agitation/aggression and euphoria compared to small vessel VaD. We expected a wide variety of symptoms in large vessel VaD, but the total NPI score and the total number of symptoms was comparable to small vessel VaD. In contrast to our results, a previous study in patients with VaD found a higher score for each symptom in large vessel compared to small vessel VaD, but without significant differences between both groups.6 However, to differentiate between small vessel and large vessel disease computed tomography was used instead of MRI, which may have influenced the subdivision of VaD patients. A high severity of agitation/aggression in VaD and specifically to large vessel VaD has been previously described.[6, 8, 10] Moreover, aggressive behaviour has been described as a possible - and if present - important clinical feature after hemispheric infarction in territories of the anterior, middle or posterior cerebral arteries.[22, 23]
Other symptoms were equally distributed between small vessel and large vessel VaD, like depressive symptoms. In accordance to the 'vascular depression hypothesis', subcortical vascular lesions frequently have been related to depression at late life, and also after ischemic stroke the risk of depression has been estimated at 33%.[24-26] In line, we found a high prevalence of depressive symptoms in both small vessel (43%) and large vessel VaD (45% of the patients).

Strengths of the current study include the large study population, as it is one of the largest clinical series of patients affected by VaD to date. Additionally, a wide spectrum of psychiatric domains was investigated using the NPI. All patients were carefully screened for fulfilment of the clinical and radiological NINDS-AIREN criteria for VaD, generally considered accurate and specific criteria. We chose to use a quite low cut-off for symptoms being classed as present/absent comparable to most other studies in the field. However, some other reports used a NPI score >4 per symptom as cut-off to define 'clinically relevant symptoms', what makes results of different studies not always interchangeable. Limitations include setting, entry criteria and other design features of a randomized clinical trial, which may have introduced a selection bias on the inclusion of patients. Although this might have led to an underestimation of symptoms, we do not believe it has played a role in the differences between small vessel and large vessel disease. Another limitation includes the study design of a cross-sectional cohort study, which precludes the assessment of causality or the evolution of symptomatology. Furthermore, the informant based structure of the NPI, which uses information of the caregiver to grade the occurrence and severity of neuropsychiatric symptoms in patients, may partially reflect coping style of the caregiver.

In conclusion, our study shows a high prevalence of behavioural and psychological symptoms amongst VaD patients, both in small and large vessel VaD. Furthermore, our results demonstrate that small vessel VaD demonstrates a different profile of behavioural and psychological symptoms compared to large vessel VaD. In particular, apathy, aberrant motor behaviour and hallucinations were more severe and more common in small vessel than large vessel VaD, possibly reflecting disruption of white matter tracts between frontal cortex and basal ganglia, while euphoria and agitation/aggression were more severe among patients with large vessel VaD. The treatment and prognostic implications of the different neuropsychiatric profiles between patients with small vessel and large vessel VaD remains to be elucidated in further research. However, recognition of these symptoms may be of importance with regard to optimizing care and determining prognosis.

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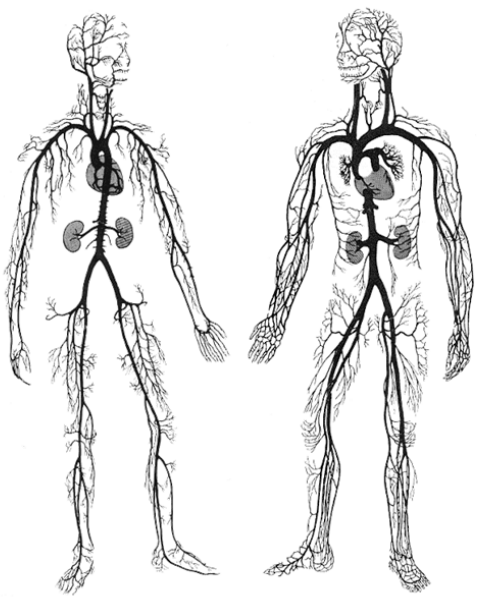
Part 6

Summary and general discussion



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The importance of vascular factors in the aging brain and dementia is increasingly being recognized. In this thesis we explored different vascular MRI measures, like total cerebral blood flow, large vessel disease and small vessel disease, in the clinical spectrum from normal aging to dementia, and we assessed relations between these MRI measures and several cardiovascular characteristics and risk factors. In addition, we aimed to get a better view of the clinical picture of dementia, determining the presence of neurological signs and neuropsychiatric symptoms in memory clinic patients and specifically in VaD, and additionally we assessed the relation between these signs and symptoms, and different MRI measures.

Summary

Cerebral blood flow in elderly

We examined the total blood flow to the brain in an elderly population in Iceland. Using 2D phase-contrast MR angiography, blood flow was measured in the basilar artery and the carotid arteries, and summed to calculate tCBF. In line with literature, increasing age was associated with a decrease in tCBF **(chapter 2.1)**.[1] Additionally, tCBF in elderly showed to be dependent on several different cardiovascular characteristics, including factors related to hematology, hemodynamics, and metabolic and cardiac disease. Moreover, some of these inverse associations with tCBF could already be found with cardiovascular characteristics assessed at mid-life, highlighting the importance to recognize cardiovascular disease early in life. Next to cardiovascular factors, it seems obvious that characteristics of the brain itself can influence blood flow due to a change of demand. TCBF is known to depend on brain volume, and with aging, brain volume decreases (i.e. due to processes such as neurodegeneration), while for example ischemic vascular lesions may progress.[2-4] We extended on previous cross-sectional studies on associations between brain volume and tCBF, by focussing in the next study on the relation between longitudinal measures of brain volume, including gray and white matter volume, WMH volume, and tCBF **(chapter 2.2)**. Relations were shown between higher annual grey matter and whole-brain atrophy and both lower tCBF and brain perfusion. Furthermore, annual progression of WMH was inversely associated with total brain perfusion, independent of age, sex and vascular risk factors. Collectively, the results suggest that brain tissue damage leads to a decreased demand for constituents of blood, implying a cycle of reduced demand and cerebral damage.

Vascular measures on MRI in mild cognitive impairment and dementia

Subsequent to aging of the general population as described above, we were interested cerebrovascular MRI changes in elderly with cognitive deficits. Although previous studies showed that both MTA and global cortical atrophy are independent predictors of progression to dementia in MCI patients, the impact of vascular disease on progression to dementia is less clear.[5-7] We examined patients with MCI and sought to determine the predictive value of cerebrovascular disease on MRI on progression to dementia **(chapter 3.1)**. Consecutive MCI patients of our outpatient memory clinic were included in the study and followed for 2 years. The presence of MTA and vascular disease (prescence of lacunes, microbleeds, infarcts, severity of WMH) was determined on baseline MRIs. In MCI patients, MTA and markers of cerebrovascular disease predicted progression to different types of dementia. MTA was a risk factor for progression from MCI to AD, while conversely the presence of cerebrovascular disease was independently associated with progression of MCI to a non-Alzheimer dementia, mostly VaD.
VaD has been reported to be the second most common type of dementia.[8] However, hardly any large studies in this patient group, e.g. on clinical or MRI characteristics, have been executed. To fill this gap of knowledge, we examined baseline characteristics of a large population VaD patients (n=706) included in a multi-center clinical trial on the effects of rivastigmine in VaD **(chapter 3.2)**. Based on MRI, patients were classified as having large vessel VaD, small vessel VaD, or a combination of both. We demonstrated that the diagnosis of VaD was in three-quarter of the patients based on small vessel disease, compared to just one fifth of the patients who fulfilled the criteria for large vessel VaD and one out of ten patients who fulfilled criteria for both types of VaD. Patients with small vessel disease were older and less educated, and showed more cortical atrophy and MTA than patients with large vessel disease. In contrast, patients with large vessel disease had more hypercholesterolemia and cardiac risk factors compared to patients with small vessel disease, illustrating heterogeneity between small vessel and large vessel VaD.

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Neurological signs in dementia in relation to MRI measures

Next, we examined clinical features, other than cognition, in dementia, and sought to determine relations between clinical symptoms and MRI measures. To start with, we assessed the presence of extrapyramidal and unilateral signs in memory clinic patients, with AD, VaD, MCI and subjective complaints **(chapter 4.1)**. Furthermore, WMH volumes on MRI were extracted automatically with a method based on a Fuzzy interference system. We found extrapyramidal signs in 10% and unilateral signs in 12% of the patients. Adjusted for age and sex, extrapyramidal signs occurred more often in VaD compared to patients with subjective complaints. Unilateral signs were more prevalent in all groups compared to patients with subjective complaints. Moreover, we found that if unilateral signs were present, patients with subjective complaints and VaD showed more WMH, whereas there was no relation in AD and MCI.

Subsequently, we examined the presence of neurological signs more extensively in VaD **(chapter 4.2)**, determining the presence of a wide range of neurological signs in a large group of VaD patients and comparing the relative frequency of specific neurological signs dependent on type of cerebrovascular disease. Literature on this interesting topic is scarce, although presence of neurological signs is required according to current diagnostic criteria of VaD.[9] We found a median number of 4.5 signs per patient, with reflex asymmetry as most prevalent symptom. Measures of small vessel disease were associated with an increased prevalence of dysarthria, dysphagia, parkinsonian gait disorder, rigidity and hypokinesia and as well to hemimotor dysfunction. By contrast, in the presence of a cerebral infarct, aphasia, hemianopia, hemimotor dysfunction, hemisensory dysfunction, reflex asymmetry and hemiplegic gait disorder were more often observed.

Neuropsychiatric symptoms in Alzheimer's disease and vascular dementia

In the final part, we determined the prevalence of behavioural and psychological symptoms, first in AD **(chapter 5.1)** and second in VaD **(chapter 5.2)**. The prevalence of symptoms was high in both populations. Additionally, both in AD and VaD, apathy was the most prevalent symptom. In AD, we found no differences in prevalence of symptoms according to MTA or WMH, as rated on MRI, suggesting that the occurrence of symptoms in AD depends on other determinants, such as coping style or genetic make-up. Relations between specific distributions of WMH or atrophy and neuropsychiatric symptoms have also been suggested, as for example more sophisticated MRI measures found neuroanatomical correlates with the prevalence of symptoms in AD, such as apathy and grey matter density loss in the anterior cingulate and frontal cortex bilaterally.[10] Future studies are needed to confirm these hypotheses. In VaD, we found that patients with small vessel and large vessel VaD demonstrated different profiles of symptoms. Especially more apathy was reported in small vessel VaD and more agitation/agression in large vessel VaD, further underlining the heterogeneity between these two groups.

Discussion

Interest in vascular factors in relation to brain aging and dementia exists since long ago, for example as described by Alois Alzheimer who published several articles on 'mental disturbances' of vascular origin between 1895-1913.[11] Alzheimer was a respected neuropathologist (as well as neurologist and psychiatrist), and tried to link clinical features with vascular pathologies of the brain. Then, with the introduction of MR imaging in the mid-eighties, the research field changed enormously. Visualization of vascular abnormalities in the brain during life helps us to learn more about the origin of these changes and their clinical consequences. Due to the relatively novelty of the technique, MR imaging itself and methods to analyze imaging files underwent rapid developments and became more and more available, making examination of large populations possible.

Striking elements of this thesis are the investigation of several vascular MR measures like total cerebral blood flow, WMH and microbleeds. Furthermore, we examined the whole spectrum of normal aging to MCI and dementia, and explored both risk factors and clinical features. First, we showed relations between cardiovascular characteristics and longitudinal brain measures and tCBF in elderly.

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Second, we demonstrated relations between vascular MRI measures and progression of MCI to dementia, and described different risk factor profiles for small vessel and large vessel VaD. Thirdly, we reported the prevalence of neurological signs and neuropsychiatric symptoms in memory clinic patients and specifically in VaD and determined relations between presence of signs and symptoms and different MRI measures. In our opinion, with these different aspects described in this thesis we contribute to the understanding of vascular changes on brain MRI and their clinical sequelae.

Methodological considerations

Selection of study population

A strong aspect of this thesis is the use of different research populations and study designs, including a population based cohort study, the study of memory clinic patients and analyses of baseline data of a large clinical trial. However, every study design has its own advantages and disadvantages. Strengths of population based studies, as applied in the first two studies of this thesis, are that besides survival bias, selection bias hardly plays a role. Furthermore, data are uniformly and prospectively collected. This allowed not only the examination of multiple cardiovascular characteristics of a large population, but additionally, with the combination of mid-life and late-life data, life course associations with tCBF could be examined. However, to gain more statistical power, for the study of diseases it is easier to examine cohorts of patients in a clinical setting. Patients visiting our outpatient memory clinic were studied to learn more about MCI and AD, and the presence of neurological signs was examined in the whole spectrum of patients with subjective complaints, MCI, AD and VaD. Prevalence of symptoms was compared between patients with subjective complaints and MCI or dementia. It must be noted that patients with subjective complaints have been shown to have a higher risk on progression to dementia compared to controls, and therefore might not be comparable to healthy aging.[12] VaD has been reported as second most prevalent type of dementia, however, the number of patients analyzed in our memory clinic was relatively small.[8] To be able to examine VaD patients more extensively, baseline data of a large multicenter clinical trial in VaD were examined, including one of the largest clinical series of patients affected by VaD to date. Nevertheless, the study design of a clinical trial may have had an effect on the inclusion of patients and perhaps has limited the possibility to generalize the results to the VaD patient group as a whole. Common to all three studies on VaD described in this thesis we found differences between patients with small vessel VaD and large vessel VaD, including differences in risk factor profiles, prevalence of neurological signs and severity of behavioural and psychological symptoms. Caution must be taken in interpretation of these results since all three studies covered the same study population, which might have had its influence on the consistency of the heterogeneity.

Diagnosis

The inevitable circularity of some studies might be a concern. In the study of MCI patients, it might not be surprising that patients with extensive vascular abnormalities on brain MRI are later diagnosed with VaD instead of AD. At baseline, none of the patients fulfilled the clinical criteria of dementia, and progression to dementia itself will not have been influenced by the MRI scan. Nonetheless, in assessing the different dementia types, MRI may have been used as a supportive element and therefore may have induced some circularity. Comparable circularity is conceivable for the study of neurological signs in VaD patients – that by definition are required to have neurological signs. However, we feel that the description of the relative frequency of a large number of neurological signs and their relations to specific types of imaged vascular damage, indeed adds to the field. Care should be taken though, that the NINDS-AIREN criteria, although generally considered accurate and specific, have been shown not to be interchangeable with other criteria for VaD.[13] Another potential limitation in the patient-related studies is misdiagnosis. Then again, all patients were carefully screened for fulfilment of current diagnostic criteria.

MRI techniques and assessments

Finally, different techniques were used to analyze the MR images. The technique we chose to measure cerebral blood flow has been shown to be non-invasive, fast and accurate.[14] On the other hand, it is a rather rough method to determine the total amount of blood flowing to the brain. To measure blood flow at brain tissue level, regional CBF per 100g brain tissue per minute can be assessed using

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techniques such as positron emission tomography or dynamic contrast-enhanced MRI. However, these techniques are invasive and complex, and difficult to use in large study populations (- an exception may be arterial spin labelling [ASL], a novel MRI technique).[15]
Structural MRI measures were assessed sometimes visually, such as counting the number of lacunes or microbleeds or using visual rating scales, and sometimes we used fully-automatic volumetric methods for example to measure WMH volumes. Although an equal validity between visual ratings scales and volumetric methods has been reported, others suggested that volumetry is more sensitive to detect small group differences.[16, 17] Finally, we used operational definitions for the NINDS-AIREN criteria for VaD, which were carefully applied by central assessment. However, the radiological criteria to diagnose VaD are known to be complex, especially for inexperienced raters.[18] A low reliability in inexperienced raters has been described, and due to these problems with applicability, comparison of our findings to other studies may be difficult.

Clinical implications

Vascular risk factors

In our study on cardiovascular characteristics, we found associations between mid-life characteristics and tCBF at late-life. Accordingly, careful control of cardiovascular risk factors early in life to prevent cerebrovascular disease appears to be an important goal for clinical practice. Additionally, strong relations between late-life cardiovascular characteristics and late-life tCBF were shown, including characteristics related to hematology, hemodynamics and cardiac function. These results underline the significance to be aware of vascular determinants in the older population and keep them in optimal condition. Ultimately, vascular risk factors may lead to such low blood flow to the brain that ischemic small vessel disease or stroke will be the consequence. Additionally, risk factors such as high blood pressure and diabetes have been associated with brain atrophy on MRI.[19, 20] Moreover, vascular disease has been shown to increase the risk of both VaD and AD.[21] For example hypertension has been reported to triple the risk of VaD, in line with our finding in VaD patients, where hypertension appeared to be the most prevalent risk factor with a prevalence of 80% in the whole cohort.[21] In patients with dementia therapeutic options are relatively scarce, and risk factor related therapy in patients who already have dementia seems a logical step to prevent further vascular damage to the brain. Effects could also be expected in AD, as vascular factors were reported to be related to disease progression.[22, 23] Nonetheless, the role of cardiovascular medications in dementia has not been firmly established yet, and results can be confusing. The use of statins and beta-blockers has been reported to slow the rate of functional decline in AD.[24] In VaD patients, the use of antiplatelet or anticoagulant medication was related to a longer life expectancy than those without.[25, 26] On the contrary, AD patients using antiplatelet therapy had no benefit, but instead the use increased the risk of serious bleedings.[27] Furthermore, anticoagulant medication has been associated to a greater risk of intracerebral heamorrhages in the presence of microbleeds on MRI, which can be of high prevalence in dementia.[28] Future research to the effects of cardiovascular medication in dementia is needed.

Clinical features

Subsequent to the relation between cerebrovascular MRI measures and cardiovascular factors, we were interested in the relation between cerebrovascular measures and clinical features in dementia. Our results indicate that next to cognitive impairment, also neurological signs, such as extrapyramidal and unilateral signs, as well as behavioural and psychological symptoms are highly prevalent in dementia. In patients with dementia, both the presence of neurological signs and neuropsychiatric symptoms have been related to a worse prognosis, higher cost of care and earlier institutionalisation.[29-31] The high prevalence of symptoms in our studies highlight the importance to recognize these symptoms in clinical practice. In VaD, we found associations between WMH and other cerebrovascular disease, and the prevalence of neurological signs and neuropsychiatric symptoms, what seems to implicate that prevention of cerebrovascular damage may lead to prevention of these signs and symptoms. In AD it seems to be more complex. We did not find a relation in AD between severity of WMH and the prevalence of neurological signs or neuropsychiatric symptoms, suggesting that in AD these signs and symptoms depend on other characteristics. Future research is needed to unravel the structural underpinnings of both neurological signs and neuropsychiatric symptoms in AD.

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Future perspectives

We examined cerebrovascular disease in the aging brain, using MRI to measure vascular changes. However, the research field is broad and there were several aspects we could not assess. For example more longitudinal research is needed to examine changes in cerebral blood flow overtime, to compare baseline and follow up blood flow and analyse intracerebral and clinical consequences of flow alterations. Furthermore, with the use of other techniques it is possible to examine brain perfusion; blood flow irrigating the brain expressed in milliliters per 100 gram of tissue per minute, corresponding to microcirculatory tissue perfusion rather than the flow of the main vascular axes. Techniques, like PET and dynamic susceptibility weighted MRI, are often complex and invasive, but hopefully will be available and applicable to large study populations one day. The same holds for novel MRI techniques, where for example diffusion tensor imaging has shown promising results to determine true white matter damage in cerebral small vessel disease, but availability of this technique needs to increase.[32]

Vascular measures

Although the radiological NINDS-AIREN criteria include important vascular disease such as infarcts, lacunes and WMH, some other measures are not incorporated. For example cortical microinfarcts seem also to contribute significantly to the progression of cognitive deficits in brain aging.[33] Additionally, microbleeds are not mentioned in the criteria, while in subcortical VaD the presence of microbleeds has been related to cognitive functioning.[34] Moreover, in our study in MCI patients, the baseline prevalence of microbleeds appeared to be higher in patients who progressed to a non-Alzheimer dementia (mostly VaD) than in patients who remained stable, which also seems to imply a relation between microbleeds and cognitive functioning. A fascinating fact regarding microbleeds is their relation to both to vascular disease and cerebral amyloid angiopathy. Cerebral amyoloid angiopathy is a cerebrovascular pathology which is found with an incidence of 80-98% in AD patients.[35] Therefore, microbleeds can potentially be regarded as the missing link between vascular disease and AD pathology. However, the origin of microbleeds in terms of risk factors and pathogenesis, as well as clinical consequences in both VaD and AD have to be elucidated in future research. Another issue include the radiological NINDS-AIREN criteria itself. The NINDS-AIREN criteria were designed in 1993, with recognition of the added value of neuroimaging.[9] At this moment, more than sixteen years later, the availability and the knowledge of brain imaging have remarkably improved. Now seems the time for a critical reappraisal of the criteria. For example involvement of at least 25% of the total white matter is considered sufficient for a diagnosis of VaD, but this percentage was set purely arbitrarily.[9] Moreover, application of this threshold is also debatable. Further work is needed to improve the quality of the radiological criteria for VaD and simultaneously increase their interobserver agreement.

Diagnosis of VaD

Proceeding with the above, the NINDS-AIREN criteria (which we used to diagnose VaD) are the diagnostic criteria that are currently most often used in VaD studies.[9] However, also other criteria such as the criteria of the International Statistical Classification of Diseases, tenth revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM IV) are in use. [31, 32] Since different criteria have been shown not to be interchangeable, comparison of different studies can be difficult.[13, 36, 37] In this day and age of globalisation, we plead for the application of only one and the same set of criteria, enabling everybody speak the same "clinical language". In addition, we believe that, next to a reappraisal of the radiological criteria, further work is needed to refine the general criteria. We showed that cerebrovascular disease underlying VaD consisted in the majority of small vessel disease. Although small vessel disease is considered to develop gradually, the NINDS-AIREN criteria require a temporal relation between evidence of vascular disease and dementia.[9, 38] In our opinion, the temporal criterion can be omitted in the criteria for small vessel VaD. Furthermore, we demonstrated several differences in risk factor and clinical profiles between patients with small vessel VaD and large vessel VaD. The difference between these two types of VaD should at least be included in a more pronounced way in new VaD criteria. Finally, currently evidence of cerebrovascular disease includes next to imaging criteria the presence of neurological signs. However, with the widespread availability of imaging nowadays to establish the presence of vascular in a more direct way, it could be argued that the criterion of neurological signs should not be required.

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VaD – AD

AD pathology and cerebrovascular disease are both very common, and as a result they inevitably occur together in many cases.[39] However, the association seems to be more complex than a mere coincidence, as there is now evidence for a significant AD – VaD overlap in terms of risk factors and clinical features. It has been suggested that AD and cerebrovascular disease may work synergistically to cause cognitive decline, but until now, it remains to be elucidated how the two interact. For example in the study of MCI patients, we found no predictive value of progression to AD of any of the vascular measures. On the other hand, in our sample VaD patients, moderate to severe MTA and cortical atrophy were shown, suggesting a relation between vascular disease and atrophy. Future research is needed to confirm our findings and further elucidate the interactions between vascular disease and AD pathology.

Clinical features

More research is necessary to the origin of clinical features in dementia. As earlier described, we did not find a relation between WMH and the presence of neurological signs or neuropsychiatric symptoms in AD patients. Possibly, in AD these signs and symptoms depend on other determinants, such as caregiver characteristics or genetic make-up. Additionally, it would be interesting to examine clinical features of AD in relation to more specific brain regions, looking at vascular disease, atrophy or regional cerebral blood flow. Recently, with the use of voxel-based-morphometry, certain foci of grey matter loss have been related to different neuropsychiatric symptoms.[10] Future studies of this kind may help to clarify the mechanisms and brain circuits involved in certain clinical features in dementia.

In conclusion, we hope that this thesis will result in further study on the significance of vascular disease in aging and dementia, emphasizing the combination of state of art novel brain imaging techniques with rigorous clinical evaluation and etiological and treatment studies.

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Conclusions

The following conclusions can be drawn from the studies presented in this thesis:

1. Total blood flow to the brain in elderly is dependent on several cardiovascular characteristics of which hemoglobin and hematocrit levels, diastolic blood pressure and cardiac disease are the most important. Additionally the associations with tCBF can be traced back to cardiovascular characteristics at mid-life.

2. Longitudinal MRI measures, as whole-brain and grey matter atrophy, and progression of WMH per year, predict total blood flow to the brain in elderly.

3. In patients with MCI, MTA and markers of cerebrovascular disease predict progression to different types of dementia. MTA is a risk factor for progression from MCI to AD, while conversely the presence of cerebrovascular disease is associated with progression of MCI to a non-Alzheimer dementia, mostly VaD.

4. Cerebrovascular disease underlying VaD consists in the majority of small vessel disease and in about one fifth of large vessel disease. Heterogeneity exist between these two groups with regard to risk factor profile and atrophy scores on MRI, the severity of the atrophy being higher in patients with small vessel disease compared to patients with large vessel disease. In contrast, patients with large vessel disease have more cardiac risk factors compared to patients with small vessel disease.

5. Neurological signs are common in a memory clinic population, but are only modestly related to WMH.

6. In VaD patients, specific neurological signs differ according to type of imaged cerebrovascular disease, with small vessel disease being often seen with more subtle signs, including extrapyramidal signs, whereas large vessel disease is more often related to lateralized sensorimotor changes and aphasia.

7. Behavioural and psychological symptoms have a high prevalence among AD patients, but there is no difference in prevalence of these symptoms according to MTA or WMH as rated on MRI.

8. In VaD, behavioural and psychological symptoms are commonly reported. Small vessel VaD and large vessel VaD show different profiles of symptoms, with especially more apathy in small vessel VaD and more agitation/aggression and euphoria in large vessel VaD.

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Nederlandse samenvatting

Van normale veroudering tot dementie;

Risicofactoren en klinische verschijnselen in relatie tot vasculaire veranderingen op MRI van de hersenen
Het aantal ouderen in de westerse wereld neemt met de vergrijzing snel toe. Als gevolg van deze vergrijzing stijgt ook de prevalentie van bepaalde ziekten, zoals bijvoorbeeld cardiovasculaire ziekte (=hart- en vaatziekte) en dementie. Het is duidelijk dat het hart en de hersenen aan elkaar gerelateerd zijn, en dat een tekort aan bloedtoevoer zal leiden tot schade in de hersenen. Een belangrijke manier om de aanwezigheid van cerebrovasculaire ziekte gedurende het leven te visualiseren en te onderzoeken, is met behulp van magnetic resonance imaging (MRI).

MRI onderzoek kan op verschillende manieren toegepast worden. Zo kan met behulp van een 2D phase-contrast MRI de bloed flow (volume van het bloed dat per tijdseenheid stroomt [eenheid = mL/min]) in de twee arteriae carotes (hals slagaderen) en de arteria basilaris (derde slagader die naar het achterste deel van de hersenen gaat) bepaald worden. Door de flow uit deze slagaderen op te tellen kan men de totale bloed flow naar de hersenen berekenen. Daarnaast kan structurele MRI gebruikt worden om de aanwezigheid van large vessel disease (schade aan de grote bloedvaten) en small vessel disease (schade aan de kleine bloedvaten) aan te tonen. Bij large vessel disease is er sprake van een (corticaal) infarct in het stroomgebied van een groot bloedvat. Belangrijke maten van small vessel disease zijn lacunaire infarcten (kleine infarcten met een maximale grootte van 1cm), microbloedingen en ischemische (ischemie=onvoldoende doorbloeding) witte stof afwijkingen (oplichtende vlekjes op de MRI scan waarvan de gedachte is dat zij veroorzaakt worden door het minder goed functioneren van de kleine bloedvaatjes in de witte stof van de hersenen, in het Engels white matter hyperintensities [WMH]).
Cerebrovasculaire afwijkingen op MRI komen veel voor bij ouderen. Verder is er aangetoond dat de prevalentie van deze vasculaire afwijkingen hoger is bij patiënten met dementie, alhoewel de klinische implicaties niet geheel duidelijk zijn.

Dementie wordt gekarakteriseerd door een verkregen stoornis van het cognitief functioneren (met betrekking tot het denkvermogen) in ten minste twee domeinen, die interfereren met het normale dagelijkse leven. Het meest voorkomende type dementie is de ziekte van Alzheimer (in het Engels Alzheimer's disease [AD]), gevolgd door vasculaire dementie (VaD; dementie veroorzaakt door schade aan de bloedvaten in de hersenen). De ervaring leert dat VaD moeilijk is te definiëren. Vroeger nam men aan dat large vessel disease de belangrijkste oorzaak was van VaD, maar het wordt steeds duidelijker dat ook juist small vessel disease een belangrijke rol speelt. De criteria van de 'National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et al'Enseignement en Neurosciences' (NINDS-AIREN) zijn op dit moment de criteria die het meest gebruikt worden voor de definitie van VaD. Mogelijk door de strikte criteria en de moeilijkheden met de definitie is er relatief weinig onderzoek verricht in de groep VaD patiënten naar bijvoorbeeld risicofactoren en klinische verschijnselen.
Het idee bestaat dat dementie zich vaak langzaam ontwikkelt en dat dit vooraf gegaan kan worden door cognitieve stoornissen die nog niet voldoen aan de criteria voor dementie. Dit stadia wordt ook wel mild cognitive impairment (MCI) genoemd. Omgekeerd bestaat het idee dat mensen die voldoen aan de criteria voor MCI, een verhoogd risico lopen op het krijgen van dementie, maar de invloed van vasculaire factoren is hierbij niet duidelijk.

Het klinisch beeld van dementie bestaat per definitie voor een belangrijk deel uit cognitieve stoornissen, zoals een stoornis van het geheugen, maar ook stoornissen van bijvoorbeeld aandacht, oriëntatie of taal komen veel voor. Daarbij wordt het de laatste tijd steeds duidelijker dat ook andere klinische symptomen belangrijk zijn bij dementie, zoals lichamelijke afwijkingen die gevonden kunnen worden bij neurologisch onderzoek, of neuropsychiatrische symptomen, zoals depressieve symptomen of agressief gedrag. Er is echter nog weinig onderzoek verricht naar de mate van voorkomen van deze symptomen bij dementie, of om welke specifieke symptomen het gaat.

Het doel van dit proefschrift was om verschillende cerebrovasculaire MRI maten te onderzoeken, zoals cerebrale bloed flow, small vessel en large vessel disease, in het klinische spectrum van normale

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veroudering tot dementie en om te zoeken naar relaties tussen deze MRI afwijkingen en mogelijke risicofactoren voor het krijgen van deze afwijkingen. Tevens wilden we een beter beeld krijgen van het klinische beeld van dementie, met betrekking tot het voorkomen van neurologische afwijkingen bij lichamelijk onderzoek en neuropsychiatrische symptomen, waarbij ook de relatie met verschillende MRI maten werd onderzocht.

Cerebrale bloed flow in ouderen

In de eerste studies onderzochten we de totale bloed flow naar de hersenen in een oudere populatie in IJsland. Met gebruik van 2D-phase contrast MR angiografie werd de bloed flow gemeten in de arteriae carotes en in de arteria basilaris en opgeteld om totale cerebrale bloed flow (tCBF) te verkrijgen. Overeenkomstig met de literatuur, vonden we dat het toenemen van de leeftijd geassocieerd was met een afname van tCBF **(hoofdstuk 2.1)**. Verder bleek tCBF op oudere leeftijd af te hangen van verschillende cardiovasculaire factoren, zoals factoren gerelateerd aan hematologie, hemodynamica en metabole en cardiale ziekte. Enkele van deze omgekeerde associaties met tCBF konden zelfs gevonden worden met cardiovasculaire factoren die bepaald waren op middelbare leeftijd. Deze bevindingen benadrukken het belang om cardiovasculaire risicofactoren vroeg in het leven te herkennen. Naast cardiovasculaire factoren lijkt het duidelijk dat ook karakteristieken van de hersenen zelf de bloed flow kunnen beïnvloeden door een verandering in vraag en behoefte. Het is bekend dat tCBF afhangt van het totale hersenvolume, en met veroudering neemt het hersenvolume af, terwijl bijvoorbeeld ischemische vaatschade zich juist kan ontwikkelen. In de volgende studie hebben we ons daarom gericht op de relatie tussen longitudinale maten van hersenvolume, zoals volumes van grijze en witte stof en ischemische witte stof afwijkingen, en tCBF **(hoofdstuk 2.2)**. We vonden relaties tussen de hoeveelheid atrofie (=afname van volume) van de grijze stof en van het globale hersenvolume per jaar, en een lagere tCBF en een lagere perfusie van de hersenen. Ook was de jaarlijkse progressie van ischemische witte stof afwijkingen omgekeerd gerelateerd aan de totale hersenperfusie, onafhankelijk van leeftijd, geslacht en vasculaire risicofactoren. Deze bevindingen suggereren dat schade aan hersenweefsel leidt tot een afname van de vraag naar bloed, wat een cirkel van afname van vraag en hersenschade doet vermoeden.

Vasculaire maten op MRI bij MCI en dementie

Volgend op veroudering in de algemene populatie zoals hierboven beschreven, waren we geïnteresseerd in cerebrovasculaire MRI veranderingen in ouderen met cognitieve problemen. Alhoewel eerdere studies reeds hebben laten zien dat zowel atrofie van de mediale temporaalkwab (MTA; de mediale temporaalkwab is een structuur aan de zijkant van het hoofd die een belangrijke rol speelt bij het functioneren van het geheugen) en globale hersenatrofie onafhankelijke voorspellers zijn van progressie naar dementie bij patiënten met MCI, is de impact van vasculaire ziekte op progressie naar dementie minder duidelijk. Wij onderzochten patiënten met MCI om de voorspellende waarden van cerebrovasculaire ziekte op MRI op progressie naar dementie te bepalen **(hoofdstuk 3.1)**. MCI patiënten van onze polikliniek werden geincludeerd in de studie en gedurende 2 jaar gevolgd. De aanwezigheid van MTA en vasculaire ziekte (aanwezigheid van lacunes, microbloedingen, infarcten, ernst van ischemische witte stof afwijkingen) werd bepaald op de baseline MRI's. We vonden dat in MCI patiënten, MTA en de maten voor cerebrovasculaire ziekte progressie naar verschillende type dementie voorspelden. MTA was een risicofactor voor progressie van MCI naar AD, terwijl de aanwezigheid van cerebrovasculaire afwijkingen onafhankelijk was geassocieerd met progressie van MCI naar een non-Alzheimer dementie, met name naar VaD.

Er wordt aangenomen dat VaD de op een na meest voorkomende dementie is. Echter, er zijn nauwelijks grote studies in deze patiëntengroep beschreven, over bijvoorbeeld klinische maten of MRI karakteristieken. Om dit gat te vullen hebben wij de baseline karakteristieken van een grote populatie VaD patiënten (n=706) onderzocht die participeerden aan een multi-center klinische trial naar de effecten van rivastigmine in VaD **(hoofdstuk 3.2)**. Op basis van de MRI werden patiënten geclassificeerd als large vessel VaD (vasculaire dementie op basis van schade aan de grote bloedvaten), small vessel VaD (vasculaire dementie op basis van schade aan de kleine bloedvaten), of een combinatie van beide. We lieten zien dat de diagnose VaD in driekwart van de patiënten gebaseerd was op small vessel disease, in vergelijking met ongeveer één vijfde van de patiënten die voldeden aan de criteria voor large vessel VaD en één op de tien die voldeden aan de criteria voor beide type VaD. Patiënten met small vessel disease

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waren ouder en hadden minder onderwijs gevolgd, en ze lieten meer corticale atrofie en meer MTA zien op de MRI dan patiënten met large vessel disease. Daarentegen, patiënten met large vessel disease hadden vaker hypercholesterolemie en vaker cardiale risicofactoren in vergelijking met patiënten met small vessel disease, wat de heterogeniteit illustreert tussen small vessel en large vessel VaD.

Neurologische symptomen bij dementie in relatie tot MRI maten

Vervolgens onderzochten we klinische verschijnselen in dementie (anders dan cognitie) en bepaalden we de relaties tussen deze klinische symptomen en verschillende MRI maten. Om te beginnen bepaalden we de aanwezigheid van extrapyramidale en unilaterale symptomen in patiënten die onze geheugen polikliniek bezochten, waaronder patiënten met AD, VaD, MCI en patiënten met subjectieve klachten (= patiënten die met klachten naar de geheugenpolikliniek komen, maar waarbij de onderzoeken niet afwijkend zijn) **(hoofdstuk 4.1)**. Tevens werden op MRI van de hersenen de volumes bepaald van ischemische witte stof afwijkingen. We vonden extrapyramidale symptomen in 10% en unilaterale symptomen in 12% van de patiënten. Gecorrigeerd voor leeftijd en geslacht, werden er meer extrapyramidale symptomen gevonden in VaD in vergelijking met patiënten met subjectieve klachten. Unilaterale symptomen hadden een hogere prevalentie in alle groepen in vergelijking met patiënten met subjectieve klachten. Daarbij vonden we dat als unilaterale symptomen aanwezig waren, patiënten met subjectieve klachten en VaD ook meer ischemische witte stof afwijkingen hadden, terwijl er geen relatie was in AD en MCI.

Vervolgens hebben we de aanwezigheid van neurologische afwijkingen bij lichamelijk onderzoek uitgebreider onderzocht in VaD **(hoofdstuk 4.2)**. Hiervoor hebben we de aanwezigheid van een groot aantal symptomen onderzocht in een grote groep VaD patiënten en de prevalentie van symptomen vergeleken aan de hand van onderliggende cerebrovasculaire afwijkingen op MRI. Literatuur over dit interessante onderwerp is zeldzaam, terwijl volgens de huidige criteria voor VaD de aanwezigheid van neurologische afwijkingen vereist is. Wij vonden een mediaan aantal van 4.5 symptomen per patiënt, met asymmetrische peesreflexen als meest voorkomende bevinding. Maten van small vessel disease waren geassocieerd met een verhoogde prevalentie van de volgende symptomen: dysarthrie, dysfagie, parkinsonachtige loopstoornis, rigiditeit en hypokinesie en ook hemimotore dysfunctie. Daarentegen, in de aanwezigheid van een cerebraal infarct werden afasie, hemianopsie, hemimotore dysfunctie, hemisensorische dysfunctie, asymmetrie van de peesreflexen en een hemiplegische loopstoornis vaker gevonden.

Neuropsychiatrische symptomen bij de ziekte van Alzheimer en vasculaire dementie
In het laatste deel van dit proefschrift hebben we de prevalentie van neuropsychiatrische symptomen onderzocht, eerst in AD **(hoofdstuk 5.1)** en daarna in VaD **(hoofdstuk 5.2)**. De prevalentie van neuropsychiatrische symptomen was in beide gevallen hoog, en zowel in AD als in VaD was apathie het symptoom wat het meeste voorkwam. In AD vonden we geen verschil in het voorkomen van symptomen in relatie tot het hebben van MTA of ischemische witte stof afwijkingen op MRI, wat suggereert dat de symptomen in AD afhankelijk zijn van andere factoren, zoals bijvoorbeeld genetische factoren. Aan de andere kant zou het ook zo kunnen zijn dat neuropsychiatrische symptomen gerelateerd zijn aan een specifieke verdeling/ specifieke locaties van atrofie of ischemische witte stof afwijkingen. Toekomstige studies zijn nodig om deze hypothese te bevestigen. In VaD vonden we dat patiënten met small vessel VaD en met large vessel VaD verschillende profielen van neuropsychiatrische symptomen lieten zien. Zo werd er vaker apathie gemeld in small vessel VaD en meer agitatie/agressie in large vessel VaD.

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Conclusies

Gebaseerd op de studies uit dit proefschrift kunnen de volgende conclusies getrokken worden:

1. De totale bloed flow naar de hersenen bij ouderen is afhankelijk van verschillende cardiovasculaire karakteristieken waarvan de waarde van hemoglobine en hematocrit, diastolische bloeddruk en aanwezigheid van cardiale ziekte het belangrijkste zijn. Daarbij kunnen de associaties met tCBF teruggevoerd worden tot cardiovasculaire karakteristieken op middelbare leeftijd.

2. Longitudinale MRI maten, zoals atrofie van het globale hersenvolume en van de grijze stof, en progressie van ischemische witte stof afwijkingen per jaar voorspellen de totale bloed flow naar de hersenen bij ouderen.

3. Bij patiënten met MCI voorspellen MTA en maten van cerebrovasculaire ziekte progressie naar verschillende type dementie. MTA is een risicofactor voor progressie van MCI naar AD, terwijl de aanwezigheid van cerebrovasculaire afwijkingen geassocieerd is met progressie van MCI naar een non-Alzheimer dementie, met name VaD.

4. Onderliggende cerebrovasculaire afwijkingen bij VaD bestaan in de meerderheid uit small vessel disease en in ongeveer één vijfde uit large vessel disease. Er bestaat heterogeniteit tussen deze twee groepen met betrekking tot risicofactor profiel en atrofie scores op MRI, waarbij de atrofie ernstiger is bij patiënten met small vessel disease in vergelijking met large vessel disease. Daarentegen, patiënten met large vessel disease hebben meer cardiale risicofactoren in vergelijking met patiënten met small vessel disease.

5. Neurologische afwijkingen bij lichamelijk onderzoek worden vaak gevonden bij patiënten die een geheugenpolikliniek bezoeken, maar ze zijn maar matig gerelateerd aan het voorkomen van ischemische witte stof afwijkingen op MRI.

6. Bij patiënten met VaD verschillen de neurologische afwijkingen bij lichamelijk onderzoek aan de hand van de cerebrovasculaire afwijkingen op MRI. Bij small vessel disease worden vaak meer subtiele symptomen gevonden, waaronder extrapyramidale symptomen, terwijl large vessel disease vaker gerelateerd is aan gelateraliseerde sensorische en motorische symptomen en afasie.

7. Neuropsychiatrische symptomen komen vaak voor bij AD, maar er is geen verschil in prevalentie van deze symptomen aan de hand van het voorkomen van MTA of ischemische witte stof afwijkingen op MRI.

8. In VaD komen neuropsychiatrische symptomen veel voor. Small vessel VaD en large vessel VaD zijn gerelateerd aan een verschillend profiel van symptomen, met met name meer apathie in small vessel VaD en meer agitatie|agressie in large vessel VaD.

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Epilogue

Het was druk aan de engelentafel, de avond dat de mens geschapen werd. 15 engelen waren van heinde en ver gekomen om over deze belangrijke zaak mee te beslissen. En ze konden het maar niet eens worden.

De eerste wilde graag acht benen, zodat er ook gemakkelijk 1 gemist kon worden. De ander stelde juist geen benen voor, zoals bij de slang gedaan was; dan kón je er ook geen missen. De meerderheid was voor iets er tussenin en na een stemming werd besloten tot 4 benen.

Engel nummer 5, een zeer praktisch ingestelde engel, stelde voor om ze niet allemaal voor het lopen te gebruiken, zodat er gelijktijdig gelopen en nog 'iets anders' gedaan kon worden. Dit idee kreeg meteen veel bijval en zo werd er al snel besloten tot 2 benen om op te lopen en 2 benen om 'iets anders' te doen. Om geen onduidelijkheid te scheppen werden de benen om 'iets anders' te doen geen benen meer genoemd maar armen.

Engel nummer 8 bedacht dat het wel handig was om ze alles te kunnen laten eten. Dus zowel planten als vlees of vis, zodat ze overal op de wereld zouden kunnen gaan wonen. Over de vacht kon men maar niet eensgezind worden. De één was voor een dikke vacht, want je moest de mensen in de kou toch beschermen. De ander vond dat weer zielig voor de mensen in de warme gebieden, die met zo'n dikke vacht waarschijnlijk niet zouden kunnen overleven. Verder was ook de kleur nog een probleem. Blauw of groen zag niemand zitten, dat zou te veel verwarring geven met het water in de zee en het gras op het land. Maar, de één wilde wit, de ander geel, rood, bruin, en zelfs zwart werd geopperd. Op een gegeven moment schreeuwde iedereen door elkaar en bijna was de vergadering in een fiasco geëindigd.

Gelukkig nam toen engel 13, zonder twijfel de slimste van het stel, het woord. "We geven de mensen geen vacht" sprak hij, "dan hebben de mensen in de warme gebieden er geen last van. De mensen in de koude gebieden zullen iets om zich heen moeten doen om zich tegen de koude te beschermen. Voordeel hiervan is, dat ze dit vervolgens makkelijk kunnen verwijderen, mochten ze zich verplaatsten naar een warmer gebied. En als we het niet eens kunnen worden over de kleur, dan maken we toch gewoon mensen in verschillende kleuren? Dat hebben we met de vogels en de vissen immers ook gedaan." En zo geschiedde.

Engel 15 was een kleine, onopvallende engel die tot dan toe nog niet gesproken had, en de enige die zich niet in alle discussies had gemengd. Hij had een beetje dromerig voor zich uit zitten staren en had zitten denken aan de dingen die volgens hem echt belangrijk waren: de nachten die hij vorige week had doorgebracht met zijn geliefde.

Engel 13, die inmiddels de taak van het voorzitterschap maar een beetje op zich genomen had, bemerkte dit ineens. "En jij daar in de hoek" bulderde hij richting engel 15. " Wat vind jij nou belangrijk voor de mens?" Nu was het muisstil en werden er 14 engelen hoofdjes naar links gedraaid.
Engel 15, geschrokken van de plotselinge aandacht, stond op van zijn kruk, rechtte zijn rug en antwoordde: "ik wil ze graag een hart geven, zodat ze van elkaar kunnen houden. En hersenen, zodat ze ook kunnen weten dat ze van elkaar houden. En tenslotte bloedvaten om het hart met de hersenen te verbinden." En zo geschiedde.

Dat het hart en de hersenen belangrijk zijn, weten we allemaal, maar toch kun je heel soms, op een mooie of juist op een tot slechte dag, deze engel nog uit de hemel horen fluisteren:
'….hart…..
hou van elkaar….
….bloedvaten
en van 't leven….
…..hersenen…..
en besef het ook……'

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Dankwoord

Ooit heb ik bedacht dat ik in iedere geval 1 boek wilde schrijven in mijn leven. Dat het een proefschrift zou worden, wist ik niet. En ook dat ik onderzoek doen zo leuk zou vinden, had ik niet bedacht. Met name het samenwerken met zoveel verschillende mensen, allemaal gefoccussed op hetzelfde doel, vond ik boeiend. Nu is het zo dat ik voor dit onderzoek enigszins in een rollende trein ben gestapt; veel zaken liepen soepel omdat anderen reeds voorwerk hadden verricht Al deze mensen die het voortbewegen van de trein mogelijk hebben gemaakt en met mij in de trein hebben gezeten ben ik zeer dankbaar.

De passagiers

Allereerst wil ik graag alle patiënten en deelnemers aan de onderzoeken die beschreven zijn in dit proefschrift hartelijk bedanken. Zonder deelnemers en patiënten geen onderzoek. Dank gaat onder andere uit naar de patiënten van de geheugenpolikliniek VUMC die hun gegevens beschikbaar stellen voor onderzoek, my thanks go out to all participants of the VantagE studies in the different participating countries, *og að lokum vil ég þakka allir sem tóku hlut (stundum mjög lengi) í Reykjavík rannsókn og siðan Reykjavík-AGES rannsókn*.

De conducteurs

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De machinist

Dr. van der Flier, **beste Wiesje**; wat een geluk heb ik gehad om onder jouw vleugels te komen werken. Ik voelde me bijzonder, soms als uitverkorene om enkele van jouw plannen waar te maken. Zonder twijfel ben jij de motor geweest achter mijn proefschrift, die mij voortdurend in de goede richting wist te krijgen. Altijd was je zeer betrokken en wist je te inspireren. Ik heb veel van je mogen leren en ik hoop dat ik dit in de toekomst ook nog kan blijven doen.

Reizen over de grens

Dr Launer, **dear Lenore**, thank you for the trust you gave me in the cerebral blood flow project. It was a great experience to work on data of such a large population based study as the AGES-Reykjavik study. Next to your extensive epidemiological knowledge, I admire your careful way of working and your talent to see with which little change the message of a manuscript can be so much clearer.

I'd like to thank dr. Jack Guralnik, dr. Tamara Harris and the other members of the Laboratory of Epidemiology, Demography, and Biometry of the NIA/NIH in Bethesda for the opportunity to work at their lab and for the pleasant athmosphere during my stay.

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Technische controle
Prof.dr. Heimans, beste Jan, bedankt voor de gelegenheid die je me biedt om tot neuroloog opgeleid te worden in het VUMC, en dank voor het deelnemen aan de promotiecommissie van dit proefschrift.

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Curriculum Vitae

Salka Sterre Staekenborg was born the 1st of July in 1980 in Utrecht, the Netherlands. After completing her high school (Gymnasium β) at the St. Bonifatius College in Utrecht in 1998, she went to Malaga, Spain, to study the Spanish language. This resulted in the fulfilment of the D.E.L.E. exam (Spaans als Vreemde Taal) in 2000 and her continuing love for the Spanish and Latin-American culture.

From 1999 to 2005 she studied Medicine at the University of Utrecht, with the completion of internships in Barcelona, Spain and Reykjavik, Iceland. After obtaining her Medical Degree, she began to work in January 2006 as a physician at the Neurology department of the VU University Medical Center. In September 2006 she started the research project, which resulted in this thesis, at the Alzheimercenter, department of Neurology at the VU University Medical Center under supervision of prof. dr. Ph. Scheltens, prof. dr. F.Barkhof and dr. WM. van der Flier.

During this period, she had the opportunity to complete a research fellowship at the Icelandic Heart Association, Reykjavik, Iceland and National Institute on Aging, Bethesda, USA, under supervision of prof. LA. Launer, supported by a grant of the Dutch Heart Organization and a Fulbright Fellowship. At the 1st of July 2009 she started her specialist registrar neurology training at the VU Universtity Medical Center.

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