Medial temporal lobe atrophy on MRI: vascular risk factors and predictive value for dementia

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Chapter 1

General introduction

Anatomy of the hippocampus

The hippocampus is a small, sea-horse-like structure in the medial temporal lobe. It is composed of the dentate gyrus, which has a folded appearance, and the cornu ammonis. These structures are curved into each other. The hippocampus is divided into the head, body and tail. The extraventricular or uncal part of the head is curved posteriorly to the parahippocampal gyrus, making the head wider compared to the other parts of the hippocampus. Towards the tail the hippocampus becomes thinner, with the tail making a curve in transverse direction. On basis of the aspect of the pyramidal neurons the cornu ammonis is subdivided into the CA1, CA2, CA3 (and CA4) area. The alveus covers the areas intraventricularly. Opposed to the CA1 area the subiculum is located, which connects the hippocampus with the entorhinal cortex.

The hippocampus is lying in the temporal horn, with the head anteriorly bounded by the amygdala, and the tail posteriorly disappearing under the splenium. Dorsally, the white matter of the medial temporal lobe is present, and ventrally the temporal stem, including the tail of the caudate nucleus and stria terminalis. Medially, the entorhinal cortex forms the border of the hippocampus. In the ventricle, the hippocampus is usually in part covered by the choroid plexus.[1]

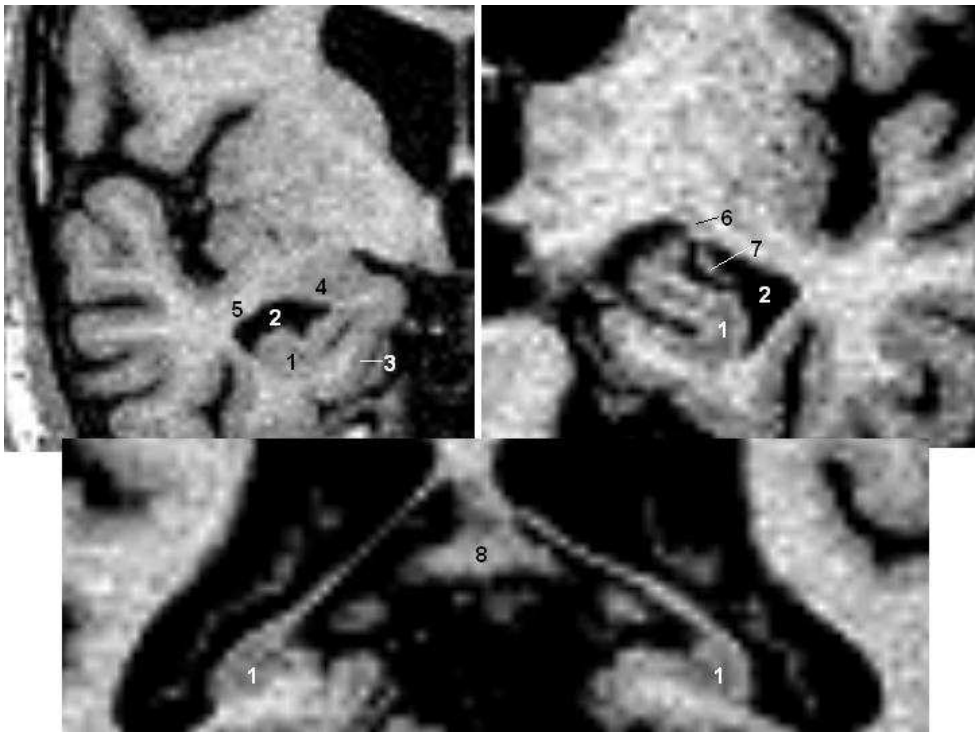

Figure 1: Coronal sections of the hippocampus on T1-weighted MRI. Left upper image most anterior, lower image most posterior slice.
1 = hippocampus; 2 = temporal horn of the lateral ventricle; 3 = entorhinal cortex; 4 = amygdala; 5 = temporal stem; 6 = tractus opticus; 7 = choroid plexus; 8 = splenium.

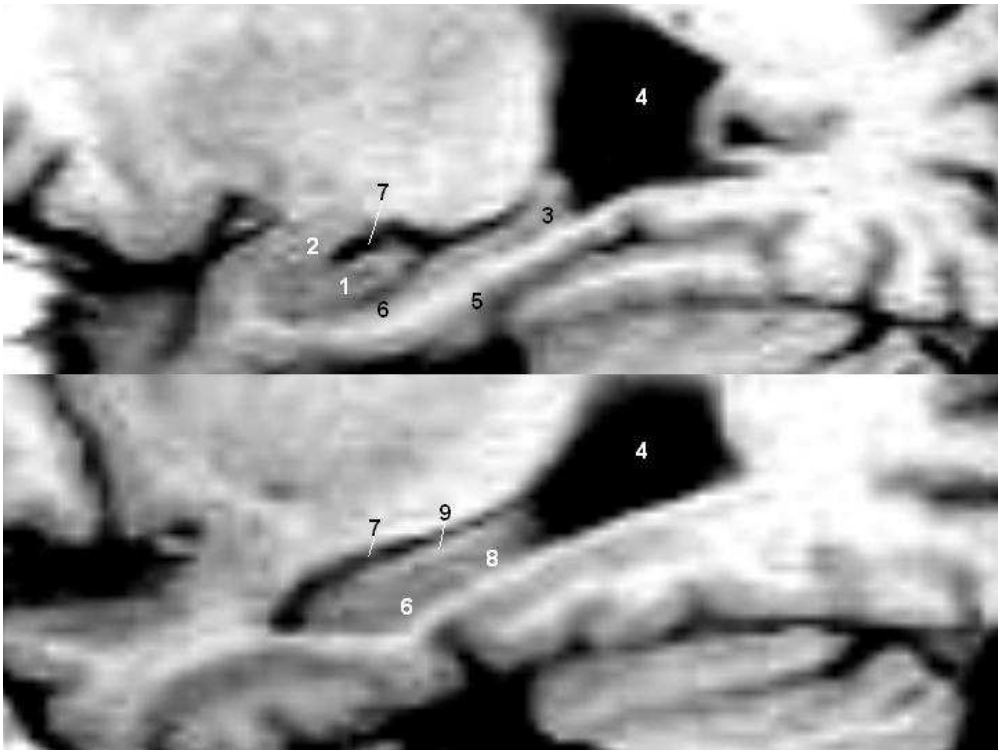

Figure 2: Sagital view through hippocampus on T1-weigthed MRI. Upper image is medial of lower image.
1 = head of hippocampus; 2 = amygdala; 3 = tail of hippocampus; 4 = lateral ventricle; 5 = parahippocampal gyrus; 6 = subiculum; 7 = temporal horn of the lateral ventricle; 8 = body of hippocampus; 9 = fimbria.

The hippocampus is vascularized by the posterior cerebral artery, who gives 3 branches (anterior, middle and posterior) to the hippocampus, and the anterior choroidal artery (uncal branch). The veins of the hippocampus drain into the basal vein.[1]

The function of the hippocampus has 4 components: learning and memory, regulation of emotional behavior, certain aspects of motor control, and regulation of hypothalamic functions.

For learning and memory, the hippocampus is embedded in two pathways: the polysynaptic pathway and the direct pathway.[2] The polysynaptic pathway gets input from the posterior parietal association cortex and neighboring temporal and occipital cortices via the entorhinal cortex to successively the dentate gyrus, CA3 area, CA1 area, subiculum, alveus and fimbria. From there, the output is projected via the fornix and the anterior thalamic nuclei to the posterior cingulated cortex and the retrosplenial cortex. The direct intra-hippocampal pathway gets its input from the inferior temporal association cortex, through the perirhinal

and entorhinal cortex to the CA1 area. From there, projections are via the subiculum and the entorhinal cortex to the inferior temporal association cortex, the temporal pole and the prefrontal cortex. The direct pathway is believed to be involved in semantic memory, the polysynaptic pathway with episodic and spatial memory.
Emotional behavior is mainly located in the amygdala, although the hippocampus may intervene in the behavior in reaction to pain. As the hippocampus is part of the ventral striatal loop, it also plays a role in the control of motor behavior. And last, the hippocampus has projections to hypothalamus nuclei and may have influence on the adrenocorticotrophic hormone production.[1]

The hippocampus, Alzheimer's disease and Mild Cognitive Impairment

The volume of the hippocampus decreases with age. Volume loss occurs mainly after the age of 55 years, although not all reports are unanimous.[3-9]
In Alzheimer's disease (AD), there is more profound atrophy of the hippocampus.[4, 10-11] AD is a neuro-degenerative disease, with neuronal loss generally assumed to start in the entorhinal cortex and the hippocampus, then spreading to the adjacent temporal, parietal and frontal neocortex. The histopathology is characterised by neurofibrillary tangles (NFT), which are mainly formed by hyperphosphoryated tau-protein, and neuritic plaques (NP), an accumulation of amyloid beta. Braak and Braak[12] staged AD on the basis of the amount and location of mainly NFT and neuropil threads.
AD is the main cause of dementia in Caucasians. It is a slowly progressive disease characterized by multiple cognitive deficits, like memory-loss, aphasia, desorientation, visuospatial disturbances and apraxia, causing disturbances in the activities of daily living. For research and clinical purposes a working group convened by the NINDS in 1983 formulated criteria that have been used ever since and have become the standard in clinical practice. In essence the criteria are as follows:[13]

- dementia established by clinical examination and confirmed by neuropsychological tests
- deficits in two or more areas of cognition, including memory impairment
- progressive worsening of memory and other cognitive functions
- no disturbances of consciousness
- age between ages 40 and 90

- absence of systemic disorders or other brain disease that in and of themselves could account for the progressive deficits in memory and cognition

In fact these criteria simply denote the presence of dementia and, in absence of another explanation, consider the dementia to be caused by AD pathology. Also, by the definition of at least two domains being affected, the pathology involves more than the hippocampal area alone. Because of the above mentioned reasons these criteria are not suitable to detect AD in an early stage.

To enable recognition of earlier stages of dementia, an entity called Mild Cognitive Impairment (MCI) was coined. It is merely a description of a state with mild disturbances in mainly one cognitive domain, without interference of daily life activities. The most widely used criteria were formulated by Ronald Petersen and these have been used in clinical research and clinical trials already.[14] They consist of the following items:

- memory complaint, preferably corroborated by an informant
- objective memory impairment
- normal general cognitive function
- intact activities of daily living
- not demented

It is widely held that amnestic MCI could signify a pre-stage of dementia, especially AD. However, there are other causes of MCI, for example depression or medication.[15] It is important to identify the subjects with a high risk of dementia, as these subjects usually want to be informed about their prognosis, and they may be selected for (pharmacologic) therapy. As the hippocampus is atrophied in AD, and is affected early in the disease process of AD, hippocampal atrophy might be a good predictor for progression to AD in MCI.

Risk factors for hippocampal atrophy

Previous research has shown several risk factors for AD. Among those are age, APOE ε4, high blood pressure and diabetes mellitus (DM).

High blood pressure has been found to be a significant risk factor for AD in longitudinal studies. In the studies based on Honolulu Asia Aging Study (HAAS) higher levels of blood pressure were found to increase the risk for clinical AD[23] and neuropathologic markers of AD.[24] In a Chinese population, high blood pressure had an odds ratio of 2 for AD.[25] In another longitudinal study, high diastolic blood pressure was associated with AD at age 79-85.[26]

The studies on DM are not conclusive. Some longitudinal studies did not find a significant relation between DM and AD,[27-29] others found an elevated relative risk of 1.5 to 2.[30-33] A recent systematic review about this association concluded that the evidence supports an increased risk for dementia in subjects with DM. This increased risk is also present for AD, although the limitations of clinical diagnostic criteria should be considered.[34] Recently, an elevated relative risk for AD was found in subjects with DM in the absence of the APOE ε4 allele.[35] This is in contrast with an earlier study of Peila et al,[33] who found a relative risk of 5.5 for AD in subjects with DM in the presence of an APOE ε4 allele.

Several studies have reported on vascular pathology, like white matter hyperintensies (WMH) and infarcts on MRI, in subjects with AD.[36-38] Also, in neuro-pathological studies, vascular lesions are frequently observed in AD brains, and include cerebral amyloid angiopathy, microvascular changes, infarction and cerebral hemorrhages.[39-41]

As AD is thought to be a neuro-degenerative disease, the finding that the presence of vascular risk factors increases the risk for AD and vascular pathology in AD, seems remarkable. These findings suggest that vascular factors might have a causative role in AD or interact with the degenerative process to cause the clinical phenotype.

It is long known that the hippocampus, especially the CA1 area, is vulnerable to ischemia.[42-45] Also, in studies with rats, hypertension has been shown to decrease hippocampal volume and number of neurons in the CA1 area.[46,47] Subjects with DM are theoretically at risk for

hippocampal atrophy, as the metabolic changes in DM could lead to the formation of NFT and NP.[48-51]

Taken together, there is reason to doubt the sole neurodegerative nature of hippocampal atrophy, and it might well be that vascular factors have a negative influence on hippocampal volume. This might have consequences for therapy, for example a more strict regulation of blood pressure and glucose in AD patients. Investigating this option would also provide a further step in understanding the etiology of hippocampal atrophy.

Measurements for estimating hippocampal volume on MRI.

Atrophy of the hippocampus can be assessed visually and volumetrically.

The medial temporal lobe atrophy scale of Scheltens[16] is regularly used as a visual method. Not only the hippocampus, but the whole medial temporal lobe is assessed on a coronal T1 weighted MRI sequence. A score from 0 to 4 is applied, dependent on the width of the choroid fissure, the width of the temporal horn and the height of the hippocampus.

This scale was first published in 1992, and is used frequently since. It has been shown to correlate well with memory performance[16,17] and volumetry,[18,19] and can distinguish AD from healthy controls.[16,20,21]

Medial Temporal lobe Atrophy scale

Score	width of the choroid fissure	width of the temporal horn	height of the hippocampus
0	N	N	N
1	↑	N	N
2	↑↑	↑	↓
3	↑↑↑	↑↑	↓↓
4	↑↑↑	↑↑↑	↓↓↓

↑ indicates increase; ↓ indicates decrease. A score of 0-4 is given separately for the left and right side.

For assessing the volume of the hippocampus, 3D T1 weighted MRI-images are reformatted to oblique coronal plane, perpendicular to the long axis of the hippocampus. The left and right hippocampal formations are measured according to criteria published by Jack et al.[22] In short, the slice on which the hippocampal formation is first visible ventral of the amygdala is the most anterior measured. The ventral border is formed by the white matter of the parahippocampal gyrus. The dorsal border is formed by the amygdala in the anterior slices; more posterior cerebrospinal fluid and choroid plexus form the dorsal border. The slice in which the crux of the fornix is visible in its total length is the most posterior slice measured. The dentate gyrus, cornu ammonis, subiculum, fimbria and alveus are included in the measurements.

Aim of the thesis

Based on the aforementioned data, we attempted to answer two questions.

Is hippocampal atrophy a good predictor for dementia in subjects with MCI?

To answer this question, we determined the MTA-score on the MRI of subjects with MCI, who visited an outpatient memory clinic, and calculated the hazard ratio of the MTA score for dementia after a mean follow-up of 34 months. This study is presented in chapter 2.

What are the risk-factors for hippocampal atrophy?

We addressed this question in different populations.

In chapter 3, the association between midlife blood pressure and hippocampal atrophy is assessed in a longitudinal, population based study (HAAS). In the analyses is accounted for possible confounders, such as socio-demographic characteristics, vascular risk factors and vascular damage on MRI, like WMH and lacunes.

In chapter 4, this association between blood pressure and hippocampal atrophy was investigated in subjects with AD. As a senile and presenile onset of dementia might represent subtypes of AD, subgroups were made on the basis of the onset of dementia. Also, subgroups were made on the presence of WMH, as WMH might be in the causal chain of the association of blood pressure and hippocampal atrophy, for example through Wallerian degeneration.

In chapter 6, the association between DM and hippocampal atrpohy was assessed in the longitudinal, population based study (HAAS). Also, other vascular pathologies seen on MRI,

like lacunes, WMH and infarcts, were assessed. The hypothesis in this study is that DM leads to both vascular as well as neurodegenerative damage in the brain.

In chapter 7, the association between DM and hypertension and hippocampal atrophy was investigated in non-disabled elderly with a wide variety in severity of WMH (LADIS). The association was also determined in the different WMH-severity groups and several socio-demographic and clinical confounders were accounted for.

The association between hippocampal atrophy and WMH is further investigated in chapter 5, were both measures are assessed at baseline and at follow-up in subjects with AD.

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Chapter 2

Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment

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Neurology 2004;63:94-100

Abstract

Background

Although detailed volumetric MRI assessment of medial temporal lobe atrophy (MTA) can predict dementia in patients with mild cognitive impairment (MCI) it is not easily applied to routine clinical practice. The objective of this study was to test the predictive accuracy of visually assessed MTA in MCI patients using a standardized visual rating scale.

Methods

Seventy-five MCI patients (mean age 63 years) underwent a coronal three-dimensional magnetization-prepared rapid gradient echo brain MRI sequence. MTA was rated visually using a 5-point rating scale.

Results

The mean follow-up period for the cohort was 34 months. At follow up, 49% of the enrolled MCI patients fulfilled criteria for dementia. MTA assessed using a standardized visual rating scale was significantly associated with dementia at follow-up, with a hazard ratio of 1.5 for every point increase in atrophy score ($p < 0.001$) and of 3.1 for the presence of atrophy based on the dichotomised atrophy score ($p = 0.003$). The predictive accuracy of visually assessed MTA was independent from age, gender, education, Mini Mental State Examination score, Clinical Dementia Rating Sum of Boxes score, verbal delayed recall, and the presence of hypertension, depression, the APOE-ε4 allele and white matter hyperintensities.

Conclusion

Visual assessment of MTA on brain MRI using a standardized rating scale is a powerful and independent predictor of conversion to dementia in relatively young MCI patients. As overlap existed in MTA scores between patients with and without dementia at follow-up, the results should be interpreted in the light of the odds for the individual patient.

Introduction

Mild cognitive impairment (MCI) is a clinical syndrome with cognitive deficits not severe enough to warrant a diagnosis of dementia. A substantial proportion of MCI patients convert to dementia, mostly Alzheimer's Disease (AD), during follow up.[1,2] Atrophy of the medial temporal lobe, including the hippocampus and entorhinal cortex, is a sensitive marker for AD.[3-9] Previous studies have shown that the volume of the medial temporal lobe is a marker for dementia in patients with MCI.[8,10-13] However, volumetric assessment of these structures is difficult to apply in routine clinical practice. Reasons include the need for digital MRI-data, the time consuming nature of region-of-interest analysis, and the fact that automated hippocampal volume measurement techniques are not widely available. By contrast the assessment of medial temporal lobe atrophy (MTA) using a standardized visual rating scale[9] is a quick and easy measurement, with a comparable predictive accuracy.[12-14] Although visually rated MTA correctly predicted outcome in 77% of the patients with MCI,[12,13] no definite conclusion regarding the clinical utility of visual MTA rating can be made. The sample size in these studies was small and did not reflect routine clinical practice because of the population-based setting or the use of multiple exclusion criteria. In addition, it has not been investigated whether qualitative MTA rating has additional predictive value over routinely used Mini-Mental State Examination (MMSE) score,[15] the Clinical Dementia Rating (CDR) Sum of Boxes score,[16] verbal delayed recall or APOE genotype, all of which are known predictors of cognitive decline.[17-20]

The aim of the current study was to test the predictive accuracy for dementia of the visual MTA score rated on routinely acquired MRI scans in a large sample of MCI patients from a secondary referral setting of a memory clinic. In addition, we investigated whether the predictive value of MTA for dementia was independent of the previously mentioned parameters. Mild depressive states are frequently seen in the pre-dementia stage of neurodegenerative disorders.[21] As the relationship between depression and hippocampal atrophy is unclear, we also included depression as a confounder in the analyses. White matter hyperintensities (WMH) on MRI are also observed in MCI patients and may contribute to cognitive decline.[22,23] Therefore, WMH was also included as confounder in our analyses.

Methods

Patients

Patients were selected from subjects that were consecutively investigated for suspected dementia at the Geriatric Clinic at Huddinge University Hospital, Stockholm, Sweden. These patients were referred by general practitioners and occupational doctors in the greater Stockholm area.

Inclusion criteria were a diagnosis of MCI (see below) at the time of the first visit and a baseline assessment between 1992 and 1997. Exclusion criteria were age below 40 years and a diagnosis of alcohol abuse according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), criteria.[24] A total of 93 patients met these criteria. MRI was performed routinely in all patients under the age of 70 years. Above 70 years of age, an MRI was done when specifically ordered by the physician for diagnostic purposes. MRI scans were available for 19 of 30 patients older than 70 years. In the subgroup of patients older than 70 years, patients without MRI did not differ from patients with MRI with respect to age, gender, years of education, length of follow-up, MMSE, CDR Sum of Boxes, verbal delayed recall, hypertension, depression, APOE genotype or decline to dementia ($p > 0.1$). Twelve subjects did not undergo MRI: 10 because they were older then 70 years and 2 because of contra-indications for MRI. Patients not undergoing MRI were older (77 vs 63 years; $p < 0.001$) and were less often female (25 vs 62% female; $p = 0.02$) than patients who had an MRI. The baseline assessment included routine MRI in all patients under age 70.

A further six patients were excluded because the follow-up was deemed too short at < 6 months. Patients lost to follow-up did not differ from the patients with a follow-up with respect to age, gender, years of education, MMSE, CDR Sum of Boxes, verbal delayed recall, hypertension, depression or APOE genotype ($p > 0.3$). The final sample thus consisted of 75 patients.

Baseline assessment

Baseline assessment consisted of general medical, neurological, psychiatric and neuropsychological investigations and brain MRI. General level of cognitive decline was assessed by MMSE[15] and by CDR.[16] APOE genotype was available for 63 patients (84%). Patients without APOE genotype assessment were older (69 vs. 62 year; $p = 0.02$) compared to patients with APOE genotype assessment, but did not differ with respect to other variables.

A diagnosis of depression[24] was considered when the Montgomory and Asberg Depression Rating Scale (MADRS)[25] score was 7 or higher. In this sample, only mild depression was diagnosed, with a maximum MADRS-score of 19.5.

Follow-up assessment

Routine follow-up appointments were made on a yearly basis until the patient fulfilled criteria for dementia or the physician considered that follow-up appointments were no longer necessary because cognitive impairment had stabilised or the patient was lost to follow-up. The follow-up assessment included a clinical interview, MMSE, CDR rating and neuropsychological assessment. No patient received a cholinesterase inhibitor during the observation period.

Diagnosis at baseline and follow-up

Patients were diagnosed with MCI if they performed 1.5 standard deviation (SD) below average for their age and education on at least one neuropsychological test, did not fulfil the diagnostic criteria for dementia according to DSM-IV criteria,[24] and did not have evidence of impairment in social or occupational functioning.[26] The overall CDR score at baseline was 0.5 for all patients. The neuropsychological tests were performed by an experienced psychologist and comprised five subtests (information, digit span, similarities, block design and digit symbol) from the Wechsler Adult Intelligence Scale-Revised,[27] Trail Making test A and B,[28] and free recall and recognition of 12 words from the Stockholm Geriatric Research Center.[27,29]

At follow-up, a diagnosis of dementia was ascertained according to the DSM-IV criteria[24] by an observer blinded to the visual MRI ratings. Probable and possible AD and vascular dementia (VaD) diagnoses were made using established criteria.[30,31]

MRI acquisition

MRI was performed using a 1.5 T system (Magnetom SP; Siemens, Erlangen, Germany). Two sequences were used: routine fast spin-echo proton density/T2 weighted (repetition time (TR) 3,500, effective echo time (TE) 19/93 milliseconds) double echo with 19 slices in the axial plane (slice thickness = 5 mm, interslice gap = 1.5 mm, field of view = 230 mm (rectangular 3/4), matrix = 192 x 256), and coronal (perpendicular to the line intersecting the

anterior and posterior commissures in the midsagittal plane) three-dimensional magnetization-prepared rapid gradient echo sequence (3D MP-RAGE, TR = 10 milliseconds, TE = 4 milliseconds, flip angle = 10°, slice thickness = 2.8 mm).

MRI readings

MTA was rated on the coronal 3D MP-RAGE images with a slice thickness of 2.8 mm. The MTA-scale[9] ranges from 0 (no atrophy) to 4 (severe atrophy) and takes into account the width of the choroid fissure, the height of the hippocampus, and the width of the temporal horn (table 1 and figure 1). The MTA-scale was applied to the right and left medial temporal lobe. In the analysis, the summed score of left and right was used as well as the dichotomised summed score (no atrophy (score 0 to 2) and atrophy (score 3 and higher)).

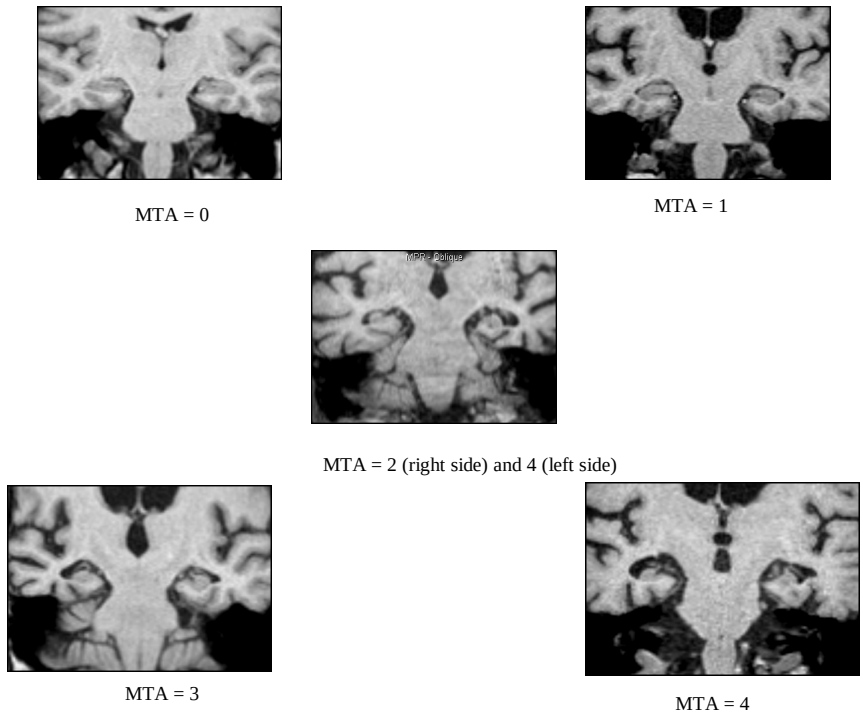
Table 1: Scheme of MTA rating.

Score	width of the choroid fissure	width of the temporal horn	height of the hippocampus
0	N	N	N
1	↑	N	N
2	↑↑	↑	↓
3	↑↑↑	↑↑	↓↓
4	↑↑↑	↑↑↑	↓↓↓

↑ indicates increase; ↓ indicates decrease. A score of 0-4 is given separately for the left and right side.

WMH were scored on the T2-weighted and proton density images. These sequences were available for 54 patients. The patients without T2 and proton density images were only different with respect to age (66 vs 61 years; p = 0.04) from the patients with these sequences. The age-related white matter changes (ARWMC) scale[32] was used to score the hyperintense deep white matter lesions in 10 different brain-regions, per region ranging from 0 to 3. For the analysis the scores of all regions were summed.

Figure 1: Medial temporal lobe atrophy scale.



The rating from 0 to 4 is displayed; higher scores indicate more atrophy. When one score is given, then left equals right.

One rater, who was blinded to all clinical information, performed all ratings. The intra-rater agreement for the summed MTA-score, determined on 20 MRI-scans, was good ($\kappa = 0.76$) and very good ($\kappa = 1$) for the dichotomised MTA-score. In an earlier study with four raters, the interobserver agreement for the MTA-score varied between a κ value of 0.34 and 0.57 and between 0.45 and 0.70 for the dichotomised MTA-score.[33] The κ value for the summed ARWMC-score was very good ($\kappa = 0.82$).

Statistical analysis

The data were analysed using SPSS version 11 (SPSS Inc., Chicago, IL, USA).

Univariate group differences were analysed by t-tests for continuous variables and χ^2 square tests with continuity correction or trend analysis for categorical data. The Z-scores of the neuropsychological tests, calculated as the difference of the individual score with the mean

score divided by the SD, were used to describe the sample in terms of cognitive deficits. Because of variability in follow-up length, the predictive accuracy of the MTA score for dementia was assessed by Cox regression analysis with follow-up time as time variable and conversion to dementia as status variable. In order to determine the odds ratio (OR), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the MTA score for dementia, logistic regression analysis was applied with outcome (dementia yes/no) at the latest available follow-up as the dependent variable. A patient was considered to have dementia predicted by the logistic regression model if the estimated probability for dementia was 0.5.

To determine the additive value of the MTA score for predicting dementia compared with potential other predictors, the MTA score was added together with one of the following variables in a Cox regression model: age (in years), gender (% female), MMSE, CDR Sum of Boxes, free recall of 12 words from the Stockholm Geriatric Research Center, presence of hypertension (either current or in the past; systolic blood pressure >140 or diastolic blood pressure >90), presence of depression, educational level (in years), presence of at least one APOE-ε4 allele and the WMH score. The hazard ratios (HR) are presented with 95% CI and significance (p value). The same analyses were performed in the subsamples of age above or below 70 years.

Results

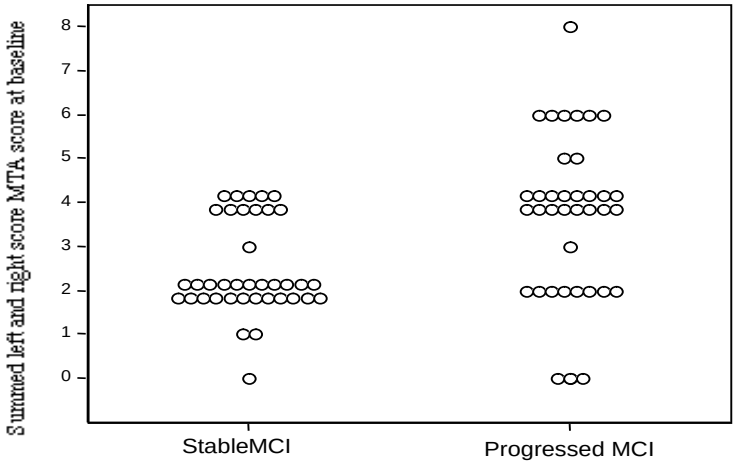
After a mean follow-up of 34 months (SD = 20.8, range = 6 to 97 months), 37 (49%) of the 75 patients had progressed to dementia; these patients are referred to as progressive MCI (PMCI). Of those, 26 (70%) had probable AD, 8 (22%) had possible AD and 3 (8%) had VaD. Patients who did not convert to dementia during the follow up period were designated as stable MCI (SMCI). Of the PMCI, 30% had amnestic MCI, 27% had a deficit in a single other cognitive domain, and 43% had deficits in multiple cognitive domains at baseline. In the SMCI group, the percentages were 24, 53 and 24. At baseline, patients with PMCI were older (p=0.03), had a higher CDR Sum of Boxes score (2.2 vs. 1.4; p = 0.002), had a lower MMSE score (26.2 vs 27.5; p = 0.05), had a lower delayed recall score (5.0 vs. 4.1; p = 0.03), and had a shorter follow-up length (28.9 vs 39.4 months; p = 0.03) than patients with SMCI (table 2). Similar results were obtained if patients with non-AD-type dementia were excluded from the PMCI group.

Table 2: Baseline characteristics of subjects with Stable MCI and Progressive MCI

	Stable MCI (n=38)	**Progressive MCI** (n=37)
Age (years)	60.6 (10.3; range 42-80))	65.2 (7.4; range 53-87)*
Gender (% women)	53	68
Follow up (months)	39.4 (23.1)	28.9 (16.7)*
Education (months)	10.5 (3.3)	9.9 (2.7)
MMSE at baseline	27.5 (3.1)	26.2 (2.5)*
CDR sum of boxes	1.4 (0.78)	2.2 (1.2) †
Verbal delayed recall	5.0 (1.4)	4.1 (1.8)*
Hypertension (%)	34	19
Depression (%)	50	33
WMH score	4.5 (6.1)	4.2 (4.9)
APOE e4 genotype (%)	42	59
MTA‡		
0	1	3
1	2	0
2	23	8
3	1	1
4	11	16
5	0	2
6	0	6
8	0	1
Dichotomised MTA		
% atrophy	32	70‡

For age, follow up, education, MMSE, CDR and WMH score the mean (SD) is presented. For MTA the numbers per score are presented.
* $p < 0.05$; † $p = 0.002$; ‡ $p = 0.001$

Figure 2: Medial temporal lobe atrophy distribution in stable MCI and progressive MCI.



On the y-axis the summed left and right MTA score is displayed in the 2 groups.

The distribution of the summed MTA score in the PMCI and SMCI is shown in figure 2. The summed MTA score and the dichotomised MTA score were both significantly associated with dementia at follow-up in the Cox regression analysis (HR = 1.5 for every point increase in summed MTA-score [p < 0.001], and HR = 3.1 for the presence of atrophy according to the dichotomised score [p = 0.003]; table 3). Similar results were obtained if patients with non-AD-type dementia were excluded from the PMCI group. The OR for progression to dementia of the summed MTA score was 1.8 (p = 0.002) for every increase in point of the summed MTA score, and 5.1 for atrophy based on the dichotomised score (p = 0.001). The sensitivity for detecting patients with dementia at follow-up was 70%, the specificity 68%, the PPV 68%, the NPV 70%, and an overall correct classification of 69% for the dichotomised score. The positive likelihood ratio for the dichotomised score was 2.19. This means that if MTA is present at baseline the pre-test odds changes from 0.96 to 2.2.

Table 3: Cox Regression: univariate analysis

	Hazard Ratio (CI)
MTA summed score	1.48 (1.19-1.84) ‡
MTA dichotomized score	3.05 (1.47-6.41) †
Age	1.03 (1.00-1.07)
Female gender	1.30 (0.64-2.64)
Education	0.93 (0.82-1.06)
MMSE	0.94 (0.87-1.02)
CDR Sum of Boxes	1.35 (1.03-1.78)*
Verbal delayed recall	1.69 (0.89-3.21)
Hypertension	0.62 (0.27-1.42)
Depression	0.76 (0.38-1.52)
APOE ε4 genotype	1.85 (0.91-3.77)
WMH	1.01 (0.94-1.08)

Cox regression with follow-up as time variable and outcome (decline to dementia) as status variable.
* p < 0.05; † p = 0.003; ‡ p < 0.001

Table 3 shows the HRs of the predictor variables for dementia from the univariate Cox regression analysis. The results of the bivariate analyses are shown in table 4. None of the variables that were added changed the HR of the MTA score for progression to dementia.

Similar results were obtained if patients with non-AD dementia were excluded from the PMCI group.

In the patients below age 70, the HR of the summed MTA score for progression to dementia was 1.41 (95% CI = 1.10-1.80), and for the dichotomised MTA score the HR was 3.25 (95% CI = 1.43-7.38). Of the other variables, only age was a significant predictor of decline (HR = 1.08, 95% CI = 1.01-1.16). In the bivariate analyses, the HR for progression to dementia of the dichotomised MTA score did not change by adding the other variables into the model one by one. In the subgroup of patients age 70 or older, only the summed MTA score significantly predicted progression to dementia (HR = 2.24, 95% CI = 1.21-4.17)). As this subgroup only consisted of 18 subjects, we did not perform bivariate analyses.

Table 4: Cox Regression: bivariate analysis

Variables	**Hazard Ratio (CI)**
MTA dichotomized score	3.09 (1.28-7.49)†
Age	1.00 (0.95-1.05)
MTA dichotomized score	3.04 (1.45-6.37)‡
Gender	1.26 (0.62-2.57)
MTA dichotomized score	2.88 (1.36-6.08)‡
MMSE	0.96 (0.86-1.06)
MTA dichotomized score	2.17 (1.01-4.65)*
CDR Sum of Boxes	1.25 (0.93-1.67)
MTA dichotomized score	2.41 (1.05-5.52)*
Verbal delayed recall	1.23 (0.62-2.45)
MTA dichotomized score	3.25 (1.39-7.63)‡
Education	0.95 (0.84-1.07)
MTA dichotomized score	3.00 (1.43-6.31)‡
Hypertension	0.66 (0.29-1.50)
MTA dichotomized score	2.91 (1.38-6.14)‡
Depression	0.87 (0.43-1.76)
MTA dichotomized score	2.84 (1.22-6.58)*
APOE ε4	1.31 (0.62-2.80)
MTA dichotomized score	3.04 (1.36-6.81)‡
WMH	1.00 (0.93-1.08)

Cox regression with follow-up as time variable and outcome (decline to dementia) as status variable.
* $p < 0.05$; † $p = 0.01$; ‡ $p < 0.01$

Discussion

In this prospective, clinically based study, we found that qualitative rating of MTA on MRI predicted conversion to dementia in patients with MCI. The predictive value of MTA was stronger than and also independent of age, gender, education, MMSE, CDR Sum of Boxes, verbal delayed recall, and presence of hypertension, depression, APOE ε4 allele, and WMH.

The fact that the qualitative rating adequately predicted dementia is in accordance with previous smaller studies.[12-14] With use of the same MTA-scale, an OR of 12.2 for decline to AD was found in an earlier study, with an overall correct classification of 77%.[12] Another group of investigators,[14] who used a qualitative visual rating of the axial aspect of the hippocampus on MRI, found an overall predictive accuracy of 91%, with a sensitivity of 91% and a specificity of 89%. The reason for the higher accuracy in this study could be that a medically healthy group of elderly patients was selected that also had a higher mean age compared to our patient sample.

The predictive accuracy in the present study was comparable to those found in volumetric MRI studies. In one study,[10] a HR of 1.45 was reported for each 1-unit decrease in the hippocampal W-score (increase in atrophy) for crossover to AD. In another study by the same research group,[19] the W scores of the baseline hippocampal volume also significantly differed between the SMCI and PMCI (-0.9 vs –1.7; p = 0.05). In another study,[8] the hippocampus and the entorhinal cortex were smaller in patients with preclinical AD compared to patients with MCI who did not progress, with a somewhat lower overall accuracy of 62% and 59%. The volume of the entorhinal cortex was found to predict conversion to AD with an OR of 0.993 (p = 0.05) for every unit decrease in entorhinal cortex volume and an overall accuracy of 78%.[11] Taken together, these data indicate that both volumetric and qualitative ratings of MTA can predict outcome in MCI patients. It should be stated, however, that in all studies, including the present one, at the individual level a considerable overlap in atrophy scores was found between the patients with stable MCI and the patients who progressed to dementia. Therefore, the score should be interpreted in the light of odds for the individual patient.

An important finding of this study is that visual rating of MTA could predict dementia independently from other known predictors of dementia. This is in agreement with a volumetric study that addressed this issue, in which the predictive accuracy of hippocampal volume was found to be independent of age, APOE genotype, MMSE, CDR and hypertension.[10] In another study, hippocampal volume as well as the MTA score also predicted AD independent from age and delayed recall.[13] The CDR sum of boxes was a

significant predictor of dementia in the univariate analyses, but lost its significance in the bivariate analyses with the MTA score, suggesting that the MTA score is a stronger predictor for dementia in this sample. Although the mean CDR sum of boxes of the PMCI was relatively high (2.2), these patients were not demented at baseline, as all patients had an overall CDR-score of 0.5 at baseline.

The proportion of patients converting from MCI to dementia was 49% over a mean duration of 34 months. This seems rather high but is in keeping with previous studies that have reported conversion rates in the same range, 22% to 72% over 3 to 4 years follow-up,[8,10,11,13,19] the range being dependent on the sample selection and age.

A remarkable observation was that the WMH on MRI as a measure of small vessel disease did not predict decline, as opposed to an earlier observation;[23] in this study, a significant difference in WMH at baseline was found between patients who developed AD and those who remained non-demented. A possible explanation for this discrepancy is that in our study, 76% of the patients had an ARWMC-score of 1 or less in any of the regions. These WMH would not be detected on CT, as used in the aforementioned study, in which WMH were found in 48% of the patients using another visual rating scale.[34] It is likely that the severity and distribution of WMH differ between these two patient-populations, which may account for the differences in predictive value.

We used dementia, and not (probable) AD, as outcome measure. The results of the analyses, after exclusion of possible AD and VaD, however, were comparable with the total sample. Because of the small sample size, separate analyses for VaD were not performed and therefore the predictive accuracy of MTA for VaD could not be assessed. It is well known however, that MTA is sensitive to, but not specific for, AD.[35,36]

Rating of the MTA score yielded a high κ value in this study. As indicated in Methods, prior studies have shown lower, but still acceptable, κ scores for intra- as well as for interobserver agreement. Variations in reliability of scoring may influence the generalizability of our findings.

A key feature of this study is the clinically based design. The study population is composed of all patients with MCI within a certain time period who visited a memory clinic for diagnostic purposes, resembling the day-to-day practice of a memory clinic. Moreover, it is a broad MCI group, not restricted to pure “amnestic” MCI, and it is a relatively large sample compared with other studies in which a visual rating scale was used.[12,13] A drawback of this clinically based design is the variability of the follow-up period; patients with stable cognitive function were discharged, or discharged themselves for several, mainly unknown

reasons. The outcome of some patients labeled as SMCI may therefore be uncertain. To address this, we performed the analyses using Cox regression to avoid overestimation of the associations. The same analyses were run with a logistic regression model (results not shown), and similar, even stronger associations were found. Another limitation is the age sampling, as patients older than 70 years only underwent MRI in case of diagnostic uncertainties. This may have biased the analyses towards higher predictive value, as these MRI scans may have been ordered because of suspected dementia. We therefore performed the analyses in the sub-sample of patients younger than 70 years of age, who all underwent an MRI routinely, and obtained similar results for the independent predictive value of the MTA score compared with the total sample. The subsample of patients older than 70 years consisted of 18 patients, enabling univariate analyses only. Although the MTA score predicted dementia in these older MCI patients the small sample size limits the generalizability of the findings.

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Chapter 3

Midlife blood pressure and the risk of hippocampal atrophy. The Honolulu Asia Aging Study.

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Abstract

Hippocampal atrophy (HA) is usually attributed to the neurofibrillary tangles and neuritic plaques of Alzheimer's disease. However, the hippocampus is vulnerable to global ischemia, which may lead to atrophy. We investigated the association of mid-life blood pressure (BP) and late-life HA in a sample of Japanese-American men born between 1900 and 1919. BP was measured on 3 occasions between 1965 and 1971. In 1994 to 1996 a subsample underwent Magnetic Resonance Imaging (MRI) of the brain. Hippocampal volume was estimated by manually drawing regions of interest on relevant scan slices; HA was defined as the lowest quartile of hippocampal volume. Also assessed on the MRI were cortical and subcortical infarcts, lacunes, and white matter hyperintensities. The risk (OR, 95% CI) was estimated for HA associated with systolic (<140 vs $\geq$ 140 mmHG) and diastolic (<90 vs $\geq$ 90 mmHG) BP, and with antihypertensive treatment. Analyses were adjusted for sociodemographic factors, other cardiovascular risk factors, apolipoprotein E allele, and correlated brain pathology. Those never treated with antihypertensive medication had a significantly increased risk for HA (OR = 1.7, 95% CI = 1.12 to 2.65)). The nontreated subjects with high systolic BP had an increased risk (OR = 1.98, 95% CI = 0.89 to 4.39) for HA. Results were similar for untreated men with high diastolic BP (OR = 3.51, 95% CI = 1.26 to 9.74). In conclusion, treatment with anti-hypertensive treatment modifies the association of BP and HA, such that high levels of BP adversely affect the hippocampus in persons never treated with anti-hypertensives.

Introduction

Damage to the hippocampus may cause anterograde and retrograde memory impairment.[1] The hippocampus and surrounding areas within the medial temporal lobe are typically involved in Alzheimer's disease (AD),[2-6] but are also affected in other dementias, such as vascular dementia (VaD).[7-10] In AD, hippocampal atrophy (HA) is usually attributed to the deposition of neurofibrillary tangles and neuritic plaques.[11,12] However, the hippocampus, particularly the CA1 area, is vulnerable to global ischemia. This vascular damage, leading to selective capillary abnormalities, neuronal necrosis, microglial and macrophage formation[13-16] may contribute to HA in both AD and VaD.

For these reasons, we investigated the association of high blood pressure (BP) and HA in a sub-sample of Japanese American men participating in the longitudinal community-based Honolulu Aging Asia Study (HAAS). Previously in this cohort, we found that hypertension in midlife increased the risk for late-life cognitive impairment, AD and VaD and for neuropathologic markers of AD.[17-20] Results, particularly for the clinical end points of AD, were strongest in those never treated for hypertension.

Methods

The design of the HAAS has been described elsewhere.[22] The original cohort included Japanese-American men born between 1900 and 1919 who underwent 5 exams (examination 1: 1965-1968; examination 2: 1968-1970; examination 3: 1971-1974; examination 4: 1991-1993; examination 5: 1994-1996). At each examination, clinical measures were made and sociodemographic and medical conditions assessed.

Dementia, blood pressure and treatment

At exams 4 and 5, cognitive status was tested with the Cognitive Abilities Screening Instrument (CASI)[23] and prevalent (examination 4) and incident (examination 5) dementia was ascertained.[22;24] Diagnostic and Statistics Manual of Mental Disorders- revised (DSM-IIIR) criteria[25] were applied for dementia, National Institute of Neurologic Diseases and Stroke—Alzheimer's Disease and Related Disorders[26] for AD, and the State of California Alzheimer's Disease Diagnostic and Treatment Centers for VaD.[27] Stroke was identified through the ongoing hospital surveillance system. Apolipoprotein E (ApoE) genotyping was performed at examination 4.[28]

We categorized BP, measured at the 3 midlife exams, as follows[17]: systolic BP (SBP): low (< 110 mmHg), normal (110 to 139 mmHg) and borderline/high (≥ 140 mmHg); diastolic BP (DBP): low (< 80 mmHg), normal (80 to 89 mmHg) and borderline/high (≥ 90 mmHg). Subjects were further classified as (n)ever treated with anti-hypertensive medication or report of treatment at any of the first 4 examinations. A new variable was created that combined treatment and mid-life BP. The BP categories were collapsed into two categories: SBP: ≥ 140 mmHg vs < 140mmHg; DBP: ≥ 90 mmHg vs < 90 mmHg. These BP categories were combined with treatment status (yes/no) to form four groups: never treated - normal, treated - normal, never treated - high, treated - high. For the analyses, the never treated - normal BP served as the reference group. Isolated high SBP was defined as SBP ≥ 140 mmHg with a DBP < 90 mmHg. Isolated high DBP was defined as DBP ≥ 90 mmHg with a SBP < 140 mmHg. These categories were also combined with treatment status in the same way as described above.

Magnetic Resonance Imaging substudy

At exam 5, an MRI study was conducted on a sub-sample,[29] including a ~10% random sample and a randomly selected oversample of those with prevalent dementia, those who scored poorly on the CASI but did not meet criteria for dementia, those with apoE ε4 genotype, and those with clinical stroke.

Scans were acquired with a GE Signa Advantage, 1.5 Tesla machine. The acquisition protocol included a T1 weighted sagital sequence, a three-dimensional coronal spoiled gradient echo sequence (SPGR), and axial T2 and proton density weighted fast-spin echo sequences.

The coronal SPGR sequence was reformatted to oblique coronal, perpendicular to the long axis of the left hippocampus. The left and right hippocampal formations were measured according to published criteria[30] and corrected for the total intracranial volume. One reader performed all measurements. The intra-class correlation coefficient for the intra-reader agreement of the hippocampal volume (HV) was 0.97. Number of lacunes, cortical and subcortical infarcts,[31] and white matter hyperintensities (WMH), graded on a scale of 0 to 9,[32] were determined.

Measures of confounding variables

Besides the variables used in sample selection, other possible confounders of the association between HA and BP were considered: education (<7 years, 7 to 9 years, > 9 years [reference]), smoking (never [reference], current and past) and daily alcohol use (none [reference], less than one drink, one or two drinks, more than 2 drinks per day).

Analytical sample

621 MRI scans were collected, and 543 MRI scans could be processed successfully for all relevant variables. The MRI sample is somewhat older (81.6 vs 79.6 years; $p < 0.001$) and had fewer years of education (10.3 vs 10.9 years; $p = 0.01$) compared to the total sample at examination 5, but did not differ with respect to BP.

Statistical analyses

We examined the relationship between BP and HV. We also created two groups, by dichotomising HV at the 25^{th} percentile; $\leq$ 25 percentile was defined as HA. ANOVA was used to test age-adjusted differences in HV by subject characteristics; Mantel-Haenszel test was used to test for differences in HA. We used a linear regression approach for HV and logistic regression approach for HA. Separate adjusted models were run for SBP and DBP, treatment status, and the combined BP/treatment variables. Three models were estimated: model 1 adjusted for age and education; model 2 also included apoE genotype, dementia status, smoking and alcohol use; model 3 we added other pathologies related to both BP and HA, including lacunes, WMH, cortical and subcortical infarcts. The interaction between high and normal levels of BP and treatment was tested by entering into model 1 the cross product between the 2 variables. Since the conclusions were similar, we present the logistic regression association (OR and 95% confidence interval [CI]) of BP with HA.

Table 1: Demographic data of MRI participants: the HAAS

Characteristic	% of subjects (n=543)	hippocampal volume(mm^3) mean (SD)	% in lower quartile of hippocampal volume
Age (years)			
<80	49.4	5583 (786)*	16.4*
>80	50.6	5202 (842)	32
Education (years)			
< 7	9.6	5120 (905)	34.6
7-9	38.3	5369 (830)	24.5
>9	52.1	5455 (820)	22.3
ApoE genotype			
33	56.2	5344 (842)	25.7
24, 34, 44	36.1	5484 (821)	21.4
22, 23	7.7	5314 (843)	26.2
Diagnosis			
Not demented	78.8	5560 (752)	16.8
AD	9.2	4631 (820)	62.0
AD+	4.2	4697 (888)	56.5
VaD	4.1	4868 (810)	40.9
Other dementias	3.7	5029 (822) *	35*
Smoking			
Never	40.1	5313 (868)	25.2
Past	31.9	5473 (773)	22.0
Current	23.2	5426 (840)	23.8
Alcohol (drinks/day)			
None	27.8	5394 (891)	21.9
<1	47.3	5434 (801)	23.0
1-2	8.3	5229 (886)	31.1
≥3	12.3	5373 (763)	25.4
WMH Grade			
1-2	53.0	5470 (815)	20.8
3	19.9	5328 (868)	26.9
≥4	27.1	5280 (844)	29.3
Lacunes			
0	56.4	5358 (856)	25.8
1-2	32.2	5428 (803)	22.3
3-5	11.4	5443 (834)	22.6
Subcortical infarcts			
0	96.3	5388 (831)	24.1
1-2	3.7	5454 (992)	30.0
Cortical infarcts			
0	91.0	5395 (828)	23.7†
1-4	9.0	5341 (926)	30.6

WMH = white matter lesions

Age adjusted p-values compared to the normal reference group:

* = <0.001; † = <0.05

Results

The mean age of the MRI sample was 81.6 years (SD = 5.0). In this sample, the left hippocampal volumes were smaller than the right hippocampal volumes (mean difference = 138 mm^3; SD = 270; $p < 0.001$). The results of the analyses for the left, right and total HV did not differ, so we only present the analyses with the total HV. HV were significantly higher in non-demented men compared those with AD, AD with cardiovascular disease, and VaD (table 1). HV was also significantly related to the CASI-score (p-trend < 0.001; table 2).

Table 2: Mean CASI-score per quartile of the hippocampal volumes: the HAAS

Quartile of hippocampal volume	CASI-score (mean (SD))
1	64.1 (20.6)
2	72.9 (13.7)
3	77.1 (11.5)
4	79.6 (11.8)

The age-adjusted test of trend is p< 0.001.

The prevalence of lacunes and infarcts was high. There was 3.7% with 1 or more subcortical infarcts, 9.0% with 1 or more cortical infarcts, and 47% had 1 or more lacunes. There was 27.3% with a WMH score of 4 or higher. There were no significant differences in HV between the subjects with and without subcortical infarcts, cortical infarcts, lacunes or WMH. However, the percentage of subjects with HV in the lowest quartile was higher in the subjects with cortical infarcts compared to the subjects without cortical infarcts (table 1).

In the total sample, DBP and SBP were not significantly associated with HA. Those not treated with antihypertensive medication, however, had a significantly increased risk for HA (OR = 1.7, 95% CI = 1.12 to 2.65), adjusting for age, education, ApoE genotype, smoking, alcohol use and dementia. Treatment history modified the association between BP and HA. Compared to the never treated - normal group, the treated men with normal or high SBP had a reduced risk (OR = 0.56, 95% CI = 0.33 to 0.97 and OR = 0.74, 95% CI = 0.42 to 1.32 respectively) for HA; the non-treated high SBP group had an increased risk (OR = 1.98, 95% CI = 0.89 to 4.39) for HA.

This same trend is seen in the DBP groups: the treated subjects with normal or with high DBP had a reduced risk (OR = 0.69, 95% CI = 0.43 to 1.12 and OR = 0.50, 95% CI = 0.24 to

1.04 respectively) and the untreated subjects with high DBP had an increased risk (OR = 3.51, 95% CI = 1.26 to 9.74) for HA compared to the non-treated subjects with normal DBP.

Table 3: Late age hippocampal volume and atrophy by mid-life blood pressure and treatment group: the HAAS

Group	Subjects (%)	Mean hippocampal volume (mm^3 (SD))	% in lower quartile of hippocampal volume
SBP (mmHg)			
<140	74.2	5402 (840)	23.3
≥140	25.8	5358 (826)	27.1
DBP(mmHg)			
<90	83.1	5392 (860)	25.1
≥90	16.9	5384 (712)	20.7
Treated with anti-hypertensives			
No	52.3	5343 (898)	28.6
Yes	47.7	5448 (757)	19.3
Not-treated 'normal' SBP	46.0	5369 (903)	26.8
Treated 'normal' SBP	28.0	5466 (717)	17.1
Not-treated high SBP	6.3	5147 (845)	42.4
Treated high SBP	19.7	5423 (813)	22.4
Not-treated 'normal' DBP	48.8	5363 (902)	27.5
Treated 'normal' DBP	34.1	5441 (790)	21.1
Not-treated high DBP	3.5	5045 (792)	44.4
Treated high DBP	13.6	5466 (671)	14.9

SBP = systolic blood pressure. DBP = diastolic blood pressure.
Treatment refers to high blood pressure treatment.
'Normal' SBP is <140 mmHg; High SBP is ≥140 mmHg; 'Normal'.
DBP is < 90 mmHg; High DBP is ≥ 90 mmHg.

The interaction between DBP and treatment was significant (p = 0.03) as was the interaction between SBP and treatment (p = 0.02). Adjusting for lacunes, subcortical infarcts, cortical infarcts or WMH did not change these associations (table 4). Regression analyses with only the non-demented subjects resulted in essentially the same associations; the OR of untreated high DBP was somewhat higher (OR = 4.76, 95% CI = 1.56 to 14.5).

Isolated high SBP and isolated high DBP were not significantly associated with HA. Compared to those with untreated normal blood pressure, there were no significant differences in HA in men with isolated systolic blood pressure who were treated (OR = 0.9, 95% CI = 0.45 to 1.81) or not treated (OR = 1.21, 95% CI = 0.49 to 3.02). Similarly, the risk for isolated DBP in treated (OR = 0.17, 95% CI = 0.02 to 1.30) and untreated (OR = 0.02, 95% CI = 0.44 to 8.42) men did not differ from those with untreated normal BP.

Discussion

In this longitudinal, prospective, population-based study we found that men never treated for high mid-life BP had an increased risk for HA compared to never treated men with normal mid-life BP. Treatment with anti-hypertensive medication reduced the risk associated with high BP. Several studies show that more hippocampal atrophy is associated with poorer cognitive function, AD, as well as other causes of dementia.[3-6;9;10;33-46]

This study has several strengths. One is the community-based sample, which has a wide range of BP and includes persons who have never been treated with antihypertensive medication despite high levels of SBP or DBP in midlife. Second, BP was measured in midlife, years before the onset of dementia. This is crucial, because dementia, as well as other factors more prevalent in old age, may lead to a lowering of BP. This decline may begin many years prior to the clinical detection of dementia. Also, BP was measured at 3 different time points, 3 times at each examination, so a reasonable estimation of average BP was obtained. Furthermore, in the analyses, we controlled for WMH and infarcts, which may mediate or confound any associations of HA to BP. Another important advantage of this study is that one rater performed the quantitative measure of the HV, with a high intrarater reliability.

However, we might have missed subjects who were treated and than stopped treatment between exams 3 and 4. Further, the men were very old at the time the MRI was made. As subjects with longstanding hypertension are likely to die at a younger age because of the adverse effects of hypertension on other organs, the effects of high BP on the hippocampus may be underestimated. In addition, within subgroups that were oversampled, those in the MRI sample may have been slightly healthier compared to subgroup members randomly selected but who did not participate.

Table 4: Risk (odds ratio (95% confidence intervals)) for late-age hippocampal atrophy by mid-life blood pressure and treatment with anti-hypertensives: the HAAS.

Group	Model 1	Model 2	Model 2 + lacunes	Model 2 + subcort inf	Model 2 + cort inf	Model 2 + WML
Not –treated 'normal' SBP	1	1	1	1	1	1
Treated 'normal ' SBP	0.58 (0.35-0.98)	0.56 (0.33-0.97)	0.60 (0.35-1.02)	0.56 (0.33-0.96)	0.55 (0.32-0.94)	0.56 (0.33-0.96)
Not treated high SBP	1.74 (0.81-3.74)	1.98 (0.89-4.39)	2.14 (0.96-4.79)	1.90 (0.85-4.24)	2.05 (0.93-4.55)	1.89 (0.85-4.22)
Treated high SBP	0.79 (0.46-1.37)	0.74 (0.42-1.32)	0.77 (0.43-1.38)	0.73 (0.41-1.30)	0.73 (0.41-1.31)	0.73 (0.41-1.30)
Not treated 'normal' DBP	1	1	1	1	1	1
'Treated' 'normal' DBP	0.73 (0.46-1.14)	0.69 (0.43-1.12)	0.71 (0.44-1.15)	0.69 (0.43-1.12)	0.68 (0.42-1.09)	0.70 (0.43-1.13)
Non treated high DBP	2.81 (1.05-7.55)	3.51 (1.26-9.74)	3.59 (1.28-10.0)	3.28 (1.17-9.19)	3.58 (1.29-9.94)	3.51 (1.27-9.75)
Treated high DBP	0.53 (0.26-1.07)	0.50 (0.24-1.04)	0.52 (0.25-1.10)	0.49 (0.23-1.02)	0.49 (0.23-1.02)	0.48 (0.23-1.01)

SBP = systolic blood pressure; DBP = diastolic blood pressure. Treatment refers to high blood pressure treatment. 'Normal' SBP is <140 mmHg; High SBP is $\geq$140 mmHg. 'Normal' DBP is < 90 mmHg; High DBP is $\geq$ 90 mmHg.

Model 1: adjusted for age and education
Model 2: adjusted for age, education, apoe genotype, smoking, alcohol and dementia.

High BP was a significant risk factor for dementia in longitudinal studies.[21;47] In the studies based on HAAS data we have found that higher levels of BP increased the risk for cognitive impairment,[17,19] clinical AD and VaD,[18] and neuropathological markers of AD.[20] In the clinical data these associations were modified by treatment status, whereby the greatest risk for adverse brain events was in those never treated with antihypertensives. The finding of a BP and treatment interaction on the risk for HA is consistent with these previously published analyses based on different measures of brain pathology.

The studies of Amenta et al and Sabbatini et al are of interest in the light of our findings.[48;49] In both studies, a group of normal rats and a group of genetically manipulated hypertensive rats were investigated. In the study of Amenta et al, hypertensive rats had reduced BP and tunica media thickness of intracerebral arteries after treatment with nicardipine, a calcium-channel blocker. In the hippocampus of the hypertensive rats, the number and size of neurons in the CA1 field were reduced compared to the normal rats, and the number of neurons in the CA1 field was increased after treatment with nicardipine. The study of Sabbatini et al also showed that the volume of hippocampi in hypertensive rates was smaller, and the volume increased when the rats were treated with antihypertensives. This volume decrease and increase was mostly explained by volume changes in the CA1 field. The treatment effects found in these animal studies are consistent with our finding that treatment was associated with a protective effect on HV. In the HAAS we do not have information on the type of antihypertensive medication that was taken nor is it known whether the treatment effect in the animals studies were specific for the nicardipine. Further research in this area is warranted.

Also of interest in light of our findings is the study of de Jong et al,[16] in which chronic brain hypoperfusion was found to cause selective capillary abnormalities in the CA1 region in rats, and the severity of capillary abnormalities was significantly related to cognitive performance. It is possible that the capillary changes precede neuronal changes and atrophy, and hypotension (i.e., caused by long-standing hypertensive vascular changes) plays a role in the atrophy of the hippocampus.

We took vascular damage in the brain into account, because it may confound or mediate the association between the HV and BP. Lacunes, subcortical and cortical infarcts, and WMH did not change the associations of interest. Earlier reports suggest that small vessel disease may be closely associated with hippocampal volume loss[39] or hippocampal hypoperfusion.[50] In this study, correction for WMH and lacunes did not alter the relation we found between BP/treatment and HV. This is in contrast to the hypothesis that hypertension influences the

WMH and hippocampus through similar mechanisms. That the mechanism of BP on HV is probably different from the hypertensive effect on WMH is supported by the findings of Fein et al.,[51] who found that WMH correlated with cortical atrophy, but not specifically with HA.
In conclusion, high levels of untreated BP was associated with HA. Treatment with anti-hypertensive treatment may modify this association.

Perspectives

HA is usually classified as a pure neuro-degenerative process. This study shows that a risk factor for vascular damage, hypertension, may also be associated with HA. The precise mechanism is unknown. Our findings should stimulate more studies to explore the effect on hippocampal atrophy of elevated levels of BP and of antihypertensive treatments. Also, other clinical and experimental studies are needed to delineate the pathophysiology of how elevated blood pressure modifies brain structure and risk for neurodegeneration. Such studies may help us to understand the etiology of the prevalent types of late-life cognitive disorders.

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Chapter 4

Blood pressure, white matter lesions and medial temporal lobe atrophy: closing the gap between vascular pathology and Alzheimer's disease?

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Abstract

Background

Vascular factors are recognized as important risk factors for Alzheimer's disease, although it is unknown whether these factors directly lead to the typical degenerative pathology such as medial temporal lobe atrophy. We set out to investigate the relation between blood pressure and medial temporal lobe atrophy in patients with senile and presenile Alzheimer's disease with or without white matter hyperintensities.

Methods

We determined the relation between blood pressure and pulse pressure and medial temporal lobe atrophy on MRI in 159 patients with Alzheimer's disease, stratified on white matter hyperintensities and age at onset of dementia.

Results

There was a linear relation between systolic blood pressure and pulse pressure (both in tertiles) and the severity of medial temporal lobe atrophy (p_{trend} = 0.05 and p_{trend} = 0.03, respectively). A significant relation was found between pulse pressure (β = 0.08 [95% CI = 0.00 to 0.15; p = 0.05] per 10 mmHg) and (borderline significant) systolic blood pressure (β = 0.05 [95% CI = -0.01 to 0.11; p = 0.1] per 10 mmHg) and medial temporal lobe atrophy. White matter hyperintensities and age-stratified analysis revealed a significant association between systolic blood pressure and pulse pressure and medial temporal lobe atrophy, only in the subsample with white matter hyperintensities and in the subsample with a senile onset of dementia. The relations were independent of severity of dementia and diabetes mellitus.

Conclusions

Systolic blood pressure and pulse pressure are associated with medial temporal lobe atrophy in Alzheimer's disease, especially in the presence of white matter hyperintensities and in patients with a late onset of dementia. Our finding may be another step in providing a rationale on how vascular factors could ultimately result in Alzheimer's disease.

Introduction

High blood pressure (BP) and atherosclerosis are increasingly being recognized as risk factors for Alzheimer's disease (AD).[1-3] The structural brain changes caused by these risk factors, such as white matter hyperintensities (WMH), lacunar infarcts and (sub)cortical atrophy can only in part explain the clinical spectrum of AD. Brain changes of vascular origin cannot account for the typical memory dysfunction in AD, which is thought to be related to medial temporal lobe atrophy (MTA). MTA is a hallmark of the pathology of AD and has proven to be a sensitive marker for the future development of AD when present on MRI scans.[4-8]

Recent studies have found a relation between increased BP levels and AD-related neuropathological changes, including an increased number of neuritic plaques (NP) and neurofibrillary tangles (NFT) in the entorhinal cortex and hippocampus of non-demented individuals.[9,10] We therefore wanted to investigate the relation between systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure, as an indicator of atherosclerosis, and MTA in patients with AD.

A previous study from our group showed that WMH are related to MTA.[11] In order to investigate whether WMH are intermediate in the relation between BP en MTA, we stratified on the presence or absence of WMH. We also performed age-stratified analysis since there is ample evidence that presentation of symptoms and the MRI characteristics differ between a presenile and a senile onset of AD.[12-14] Since dementia severity and diabetes mellitus (DM) are both related to the determinant and the outcome (and are not in the causal chain), they may act as a confounder[3,15-22] and were both adjusted for in the analyses.

Methods

Patients

Patients were selected from individuals that were consecutively investigated for suspected dementia at a secondary/tertiary referral Alzheimer Center. We identified 159 patients with AD in a 2-year period, who underwent a standardized work-up, involving history taking, physical and neurological examination, blood tests (erythrocyte sedimentation rate, haemoglobin, white cell count, serum electrolytes, glucose, urea, creatinine, liver function tests, Thyroid Stimulation Hormone and free thyroid hormone, vitamin B1 and B6 levels, syphilis serology), Mini Mental State Examination (MMSE), neuropsychological examination, MRI of the brain and a quantitative EEG. Final diagnosis was based upon a

consensus meeting, attended by at least a neurologist, neuropsychologist, radiologist, clinical neurophysiologist, geriatrician and specialized nurse, where all the available clinical data and the results of the ancillary investigations were considered. A diagnosis of probable AD was based upon the NINCDS-ADRDA criteria.[23]

MRI

All patients underwent cranial MR imaging including coronal T1-weighted and transverse proton density (PD) or fluid attenuated inversion recovery (FLAIR) images on a 1.0-tesla scanner (Impact, Siemens AG, Germany) or a 1.5-tesla scanner (Vision, Siemens AG, Germany). Slice thickness of the transverse PD and FLAIR was 5 mm with an inter-slice gap of 20.0%. Slice thickness of the coronal T1 weighted sequence was 1.5 mm without inter-slice gap.

MTA and WMH rating scale

MTA was rated on the T1-weighted coronal images using the MTA-scale[17]: this scale ranges from 0 (no atrophy) to 4 (severe atrophy), and takes into account the width of the choroid fissure, the height of the hippocampus, and the width of the temporal horn. The MTA-scale was applied to the right and left medial temporal lobe and the mean of these two measured was used in the analysis. Previous studies showed a fair to moderate inter-rater agreement (κ value 0.3 to 0.6)[24] and a good intra-rater agreement with a κ value of 0.8[25] for the MTA score. The MTA is significantly correlated with memory function[16,17] and shows a good relation with volumetry.[26,27] MTA is also a predictor of AD in patients with mild cognitive impairment.[7,8,25] WMH were rated with the age-related white matter changes (ARWMC) rating scale.[28] In short: WMH on MRI are defined as ill-defined hyperintensities of ≥ 5 mm on PD or FLAIR images, and are rated on a four-point scale in five different regions in the left and right hemisphere separately: (1) the frontal area; (2) the parieto-occipital area; (3) the temporal area; (4) the infratentorial area and (5) the basal ganglia and scored semi-quantitatively as 0 (no WMH), 1 (single or multiple focal lesions ≥ 5 mm), 2 (beginning of confluence of lesions) or 3 (confluent WMH). Total degree of WMH was calculated by adding the region-specific scores of both hemispheres (range 0-30). WMH could not be rated in 8 patients due to poor scan quality (movement artefacts).

One rater, blinded for BP measurements, scored the WMH and the MTA with good to excellent intra-rater agreement (κ = 0.70-1.0 and κ = 0.6-0.8, respectively).

Blood pressure

BP level was based on a single measurement with the patient in sitting position. The first and the fourth Korotkoff tone were used for the SBP and DBP, respectively. Pulse pressure was defined as the difference between SBP and DBP. Information on treatment for high BP was collected by a structured interview.

Other variables

Global dementia severity was estimated with the MMSE.[29] Presence of DM was defined by the use of oral anti-diabetics or insulin, and was previously assessed by the general practitioner or by a specialist in internal medicine by applying standard methods.[30] In the present sample, no subjects with newly discovered DM were included.

Statistics

Age-adjusted differences in subject characteristics were examined across subgroups using analyses of variance if the characteristic was continuously distributed and with Mantel-Haenszel test if it was categorical. We calculated regression coefficients (with 95% CIs) by means of age and sex adjusted multiple linear regression analysis to quantify the relation between BP, pulse pressure and MTA. The interaction between SBP and WMH was tested by entering the cross product between the two variables into the model. Likewise, the interaction between pulse pressure and WMH, DBP and WMH, SBP and age at onset of dementia, DBP and age at onset of dementia, and pulse pressure and age at onset of dementia was tested.

Secondly we investigated the relation between BP and pulse pressure and MTA stratified on the presence of WMH. Total WMH was dichotomised into no WMH (score 0) and any WMH (score > 0). Thirdly, we stratified on the age at onset of dementia. Presenile onset of AD was defined as the first symptoms of cognitive decline occurring before the age of 65 years.[12,31]

In order to gain statistical power and to increase contrast between groups, means of the left and right MTA scores were divided into 4 categories[11]: score 0-0.5 (n = 23); 1-1.5 (n = 66); 2-2.5 (n = 56); 3-4 (n = 14). Tests for trend were calculated by inserting tertiles of BP and pulse pressure as continuous variables in the multivariate models.

These relations may be confounded by dementia-severity or DM. We therefore included the MMSE and DM as possible confounders in the models.

Table 1: Baseline characteristics for the whole study population and stratified on WMH and age.

	Total sample (n=159)	WMH absent (n=108)	WMH present (n=43)	Presenile (n=66)	Senile (n=93)
Age (years)	68.3 (8.8)	67.1 (8.9)	71.3 (8.0)[a]	59.2 (5.4)	74.5 (4.2) [b]
Sex (% female)	49.7	50.9	48.8	55.4	45.7
Duration of symptoms (years)	2.6 (1.9)	2.6 (1.9)	2.6 (1.6)	2.9 (2.1)	2.4 (1.7)
MMSE	20.7 (5.1)	20.6 (5.2)	21.1 (4.8)	19.0 (4.6)	21.7 (5.1)[c]
SBP (mmHg)	149.2 (22.5)	149.1 (20.9)	152 (25.6)	141.8 (20.7)	154.4 (22.3)[b]
DBP (mmHg)	86.0 (11.4)	86.5 (11)	85.9 (11.6)	85.8 (11.8)	86.1 (11.1)
Pulse pressure (mmHg)	63.2 (17.7)	62.6 (16.0)	66.1 (20.6)	56 (14.5)	68.3 (18.0)[b]
Treatment for high BP (%)	19.0	14.0	32.6[d]	12.5	23.4
DM (%)	5.6	5.9	6.1	2.0	8.1
WMH-score					
ARWMC = 0 (%)	71.5	100	0	82.3	64.0[e]
ARWMC > 0 (%)	28.5	0	100	17.7	36.0
Mean MTA score (%)					
0-0.5	14.5	18.5	7.0[f]	19.7	10.8[g]
1-1.5	41.5	47.2	27.9	51.5	34.4
2-2.5	35.2	28.7	55.8	24.3	43.0
3-4	8.8	5.6	9.3	4.5	11.8

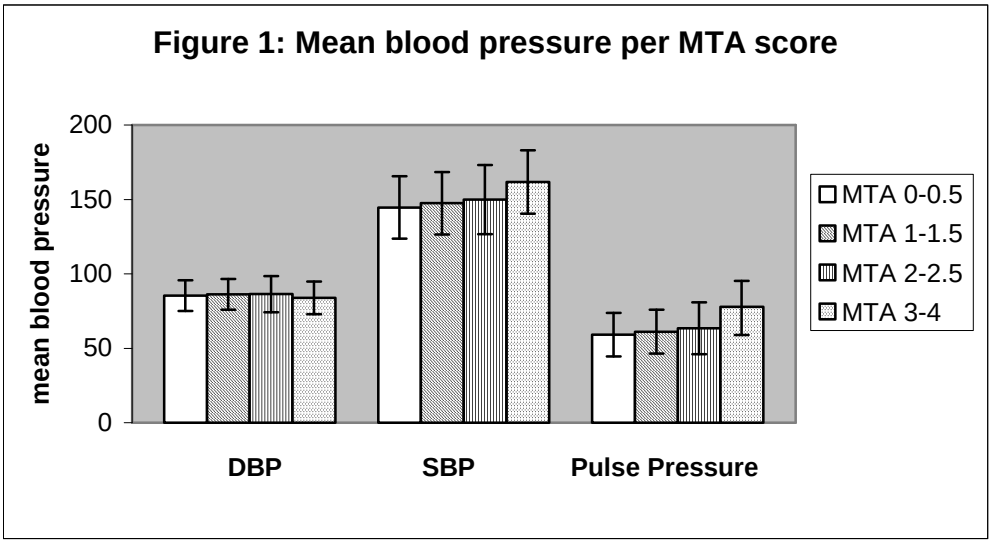
Baseline characteristics of the study population, stratified on WMH and on the age of onset of dementia. Values represent means (SD) or percentages. WMH rating missing in 8 patients. Age-adjusted differences in subject characteristics were examined across subgroups using analyses of variance if the characteristic was continuously distributed and with Mantel-Haenszel test if it was categorical.

WMH- = the sub-sample without WMH; WMH+ = the sub-sample with WMH; Presenile = the sub-sample with a presenile onset of dementia; Senile = the sub-sample with a senile onset of dementia; WMH-score = total ARWMC-score.
[a]: $p = 0.009$ compared to WMH-; [b]: $p < 0.001$ compared to presenile; [c]: $p = 0.004$ compared to presenile; [d]: $p = 0.01$ compared to WMH-; [e]: $p = 0.02$ compared to presenile; [f]: $p = 0.002$ compared to WMH-; [g]: $p = 0.002$ compared to presenile

Results

Baseline characteristics are listed in table 1. Mean age was 68.3 years (range 49 to 89 years), almost 50% of the subjects were female. High DBP (> 90 mmHg) was present in 24.5% of the patients, whereas 57.9% had a high SBP (>140 mmHg); 19% of the patients were currently treated for high BP. Of the patients with high SBP, 75% received no treatment with anti-hypertensive medication. Of the patients with a high DBP, 64.1% received no treatment for high blood pressure. Of all patients, 71.5% had no WMH, and 44% had a mean MTA score of 2 or higher. The mean BP in the separate categories of MTA is represented in figure 1.

Figure 1: Mean blood pressure (SBP, DBP and pulse pressure) per MTA score.



MTA score grouped as follows: 0 = 0-0.5; 1 = 1-1,5; 2 = 2-2,5; 3 = 3,5-4

The 43 patients with WMH had a median WMH-score of 2 (range 1 to 13). The patients with WMH were older (71.3 [SD = 8.0] vs 67.1 [SD = 8.9] years, p = 0.009), had more MTA (p = 0.002) and were more frequently treated for hypertension (32.6% vs 14%; p = 0.01) compared to the patients without WMH. There was no difference in BP between the groups with and without WMH. The patients with a presenile onset of dementia had a lower MMSE (19.0 [SD = 4.6] vs 21.7 [SD = 5.1], p = 0.004), a lower SBP (141.8 [SD = 20.7] vs 154.4 [SD = 22.3] mmHg, p = 0.001), a lower pulse pressure (56 [SD = 14.5] vs 68.3 [SD = 18.0] mmHg, p = 0.001), less WMH (p = 0.02) and less MTA (p = 0.002) compared to the patients with a senile onset of dementia.

There was a significant relation between pulse pressure (β = 0.08 [95% CI = 0.00 to 0.15, p = 0.05] per 10 mmHg pulse pressure,) and (borderline) SBP (β = 0.05 [95% CI = -0.01 to 0.11, p = 0.1] per 10 mmHg) and MTA, respectively, whereas this was not found for DBP (table 2). Tests for trend revealed a significant relation between SBP and pulse pressure in tertiles and the severity of MTA (p_{trend}=0.05 and p_{trend} 0.03, respectively).

Table 2: Relation between blood pressure, pulse pressure and medial temporal lobe atrophy.

	Total sample	WMH -	WMH +	Presenile	Senile
SBP	0.05 (-0.01–0.11)	0.01 (-0.07-0.09)	0.12 (0.03-0.21)[a]	0.01 (-0.09-0.1)	0.10 (0.007-0.19)[b]
DBP	0.008 (-0.11–0.12)	0.006 (-0.13-0.14)	0.07 (-0.15-0.28)	-0.03 (-0.21-0.14)	0.02 (-0.16-0.20)
PP	0.08 (0.00-0.15)[c]	0.01 (-0.09-0.12)	0.16 (0.05-0.27)[d]	0.04 (-0.1-0.18)	0.10 (0.02–0.22)[e]

Multiple linear regression analyses between systolic blood pressure (SBP), diastolic blood pressure (DBP) or pulse pressure (PP) and medial temporal lobe atrophy, adjusted for age and sex, for the study population as a whole and stratified on the absence or presence of WMH and on the age of onset of dementia. Values represent the beta-coefficients per 10 mm Hg blood pressure with 95% confidence intervals.
[a] p = 0.01; [b] p = 0.04; [c] p = 0.05; [d] p = 0.006; [e] p = 0.03

Stratification on WMH revealed a significant association between MTA and SBP (β = 0.12 [95% CI = 0.03 to 0.21, p = 0.01] per 10 mmHg) and pulse pressure (β = 0.16 [95% CI = 0.05 to 0.27, p = 0.006] per 10 mmHg), respectively, which was only present in patients with WMH, and not in those without (table 2). The interaction between SBP and MTA (p = 0.05) and between pulse pressure and MTA (p = 0.05) was significant. Stratification on the age at onset showed a significant association between MTA and SBP (β = 0.10 [95% CI = 0.007 to 0.19, p = 0.04] per 10 mmHg) and pulse pressure (β = 0.10 [95% CI = 0.02 to 0.22, p = 0.03] per 10 mmHg) respectively, only in those patients with a senile onset of dementia. This was independent from WMH severity. Additional adjustments for MMSE and DM did not alter the magnitude of the associations.

Discussion

We found that pulse pressure and SBP were significantly related to MTA-severity in patients with AD, especially in the sub-group with WMH and in those with a senile onset of dementia.

One of the strong points of our study is the large sample of exclusively mild affected AD patients. Furthermore, all patients underwent standardized MRI scanning, and both WMH and MTA were rated by a single rater with high intra-observer reliability, with the aid of a visual scale that has been shown to have a good correlation with volumetry.[26,27] In addition, all patients were diagnosed within the same setting by a small group of experienced investigators, minimizing diagnostic uncertainty and heterogeneity of the sample.

However, some methodological issues need to be considered. Our study had a cross-sectional design. Therefore a causal relationship between BP, pulse pressure and MTA cannot be inferred. However, the dose dependent relation between BP, pulse pressure and MTA suggests causality.

Selection bias may have occurred since the level of BP may be related to the accessibility of the outpatient clinic for patients with AD. It may be that those with the highest BP suffer more from cardiovascular complications and WMH that prevent them from visiting an outpatient clinic, for example due to gait disturbances.[32-34] Similarly, it seems plausible that patients with the most severe MTA suffer from the most severe dementia, and as a consequence are more institutionalized. Such patients may be presumed to visit an outpatient memory clinic less often. Consequently, patients with the highest BP and those with the most severe MTA might be underrepresented, and therefore may have biased the outcome.

The degree of MTA was less than one would expect in an AD-sample. AD with a presenile onset usually presents with visuo-spatial defects, whereas memory dysfunction occurs later in the disease process. Since MTA is thought to be related to memory dysfunction, it could be that MTA would occur later in the disease process. In the present sample there is a relative large sub-sample of presenile AD patients (41.5%) with a relative high MMSE possibly explaining the rather mild degree of MTA. The fact that MTA increases with progression of dementia,[35-37] and the present sample includes mainly mild demented subjects may explain the rather mild MTA in the present sample.

We only found a relation between SBP and MTA, and not between DBP and MTA. A possible explanation may be that DBP is not a good indicator for vascular events in the elderly.[26,31] This may be due to a decrease in DBP after the age of 50-60,[38] especially among individuals with atherosclerosis. Our finding of an association between MTA and SBP and not with DBP is consistent with this notion. On the other hand SBP has also been shown to decrease with aging, and even disproportionably more in patients with dementia, and dementia-severity.[3,39] Therefore, we included age and MMSE as an indicator of dementia severity in our models, but this did not alter the magnitude of the association.

The relation between BP and MTA was only present in the patients with a senile onset of AD. A possible explanation may be that BP differentially affects the hippocampus in patients with senile or presenile AD, or that BP is only related to MTA in senile AD. These data underscore the existence of subtypes of AD, among others based on the age of onset and vascular comorbidity. This subdivision had already been suggested by Alzheimer himself but is barely recognized in current studies.[40]

In the present study, the association between SBP, pulse pressure and MTA was most outspoken in the subgroup with WMH, suggesting that certain brains are more susceptible to vascular factors than others, and that MTA in the absence of WMH has a different pathologic substrate, which is probably not vascular.[33] A possible mechanism could be that increased BP levels cause MTA and WMH by inducing micro vascular changes. However, adjustment for the severity of the WMH did not change the magnitude or strength of the association between BP and MTA, suggesting that the mechanism of the effect of BP on WMH and MTA is different, although both may be a downstream effect of, for example, atherosclerosis.

Several mechanisms for the relation between BP and MTA have been suggested. Previous studies have shown that high BP is related to an increased number of NP and NFT in the hippocampus.[9,10] Possibly, high BP results in an impaired cerebral blood flow and subsequently affects the CA1 area in the hippocampus, which is known to be very sensitive to ischemia, resulting in atrophy of the medial temporal lobe.[41-43] Another explanation could be that a common agent affects both BP and MTA: possible candidates inlude angiotensin converting enzym and vasopressin, as well as genetic factors.[44,45]

In conclusion, we found that SBP and pulse pressure were associated with MTA in patients with AD, especially in those with a senile onset or in those with WMH. Our finding may be another step in providing a rationale on how vascular factors could ultimately result in AD. It also fuels the notion that treatment of hypertension may be important for the prevention of dementia.[46] Large prospective studies are needed to unravel the chain of events from elevated BP to MTA and the development of AD.

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Chapter 5

White matter lesions are associated with progression of medial temporal lobe atrophy in Alzheimer's disease.

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Abstract

Background and purpose

Medial temporal lobe atrophy (MTA) is a hallmark of Alzheimer's disease (AD). Its progression is often seen during the course of AD, but its frequency and risk factors remain unclear.

Methods

We investigated this in 35 AD patients from whom sequential MRI scans were available. White matter hyperintensities (WMH; for the periventricular (PV) and subcortical (SC) region separately) and MTA were rated semi-quantitatively.

Results

In approximately two thirds of all patients progression of MTA was found. The mean MTA progression was 0.8 (SD = 0.5) and 0.3 (SD = 0.4) for patients with or without PVWMH at baseline (p = 0.01). Patients who showed progression of PVWMH over the course of their disease had a significantly higher mean progression of MTA than those without PVWMH progression (0.9 (SD = 0.4) and 0.4 (SD = 0.5, p = 0.01). Patients with PVWMH at baseline had a 40-fold increased risk for progression of MTA compared to those without baseline PVWMH (OR = 40.0, 95% CI = 1.3 to $1.2x10^3$, p = 0.03). Patients with progression of PVWMH during the course of the disease had an increased risk for MTA progression (OR = 3.7 per unit increase of progression of PVWMH, 95% CI = 1.1 to 12.9, p = 0.04). There was higher risk for progression of MTA for those with progression of PVWMH than those without (OR = 10.9, 95% CI = 1.0 to 122.5, p = 0.05). This was not found for SCWMH.

Conclusions

Our findings suggest that the presence and the progression of WMH are associated with progression of MTA in AD. WMH may be a predictor of the course of the disease and a potential treatment target in AD.

Introduction

Medial temporal lobe atrophy (MTA) is one of the first changes seen in the brains of Alzheimer's Disease (AD)[1] patients. Its presence has proven to be a sensitive marker for the diagnosis of AD and also for future development of AD in patients with mild cognitive impairment.[2,3] Progression of AD is paralleled by progression of MTA.[4] There is very little known on factors that influence MTA progression.

Observational studies show an increased burden of amyloid plaques and neurofibrillary tangles by severity of MTA during the course of the AD,[1] but prospective follow-up studies on the frequency and risk factors for MTA progression in order to assess causality are lacking. Identification of potential modifiable risk factors for MTA progression is of importance to help advise patients and their relatives on what to expect from the disease in the near future and in terms of potential future treatments.

Potential risk factors for MTA progression include white matter lesions (WMH) in view of a recently described relation between WMH and MTA in a cross-sectional study.[5] Given that in the course of AD WMH also progress over time[6] progression of WMH may also be a risk factor for progression of MTA. If a causal relation between WMH and MTA progression is to be proven MTA progression may be prevented by modifying the progression of WMH by for example treatment of the vascular risk factors for WMH such as hypertension.

We hypothesized that the presence of WMH at baseline and their progression along the course of AD are associated with MTA progression. We therefore wanted to investigate the frequency distribution of MTA progression among AD patients and the relation between baseline and progression of WMH and the progression of MTA in a prospective cohort of AD patients.

Methods

Study population

We investigated AD patients from a prospective study on AD at the secondary/tertiary referral Alzheimer Center of the VU University Medical Centre in Amsterdam who all underwent serial MRI scanning. As part of a routine diagnostic procedure all patients underwent a standardized work-up involving history taking, physical and neurological examination, blood tests (Erythrocyte Sedimentation Rate, haemoglobin, white cell count, serum electrolytes, glucose, urea, creatinine, liver function tests, Thyroid Stimulation Hormone and free thyroid

hormone, vitamin B1 and B6 levels, lues reactions), Mini Mental State Examination (MMSE),[7] neuropsychological examination, structural imaging of the brain and a quantitative EEG. Final diagnosis was based upon a consensus meeting where all the available clinical data and the results of the ancillary investigations were considered. A diagnosis of probable AD was based upon the NINCDS-ADRDA criteria.[8] All patients provided written informed consent for their clinical data being used for research. We identified 35 out of 252 consecutive patients with 'probable'AD who had serial MRI scans available (mean follow-up 2.2 years (range: 1.0-5.1 year)).

Magnetic resonance imaging study protocol

All subject underwent a cranial MRI including coronal T1-weighted and transverse proton density (PD) or fluid attenuated inversion recovery (FLAIR) images on a 1.0T scanner (Impact, Siemens AG, Germany) using a standardized protocol, including contiguous 3mm thick slices for the T1-coronal images and 5 mm thick slices, with an inter-slice gap of 20.0%, for the PD and FLAIR images. All sequences yielded an in-plane resolution of 1x1 mm^2. The second scan was made on the same machine with identical protocol. The images were printed as hard copy with a reduction factor of 2.7.

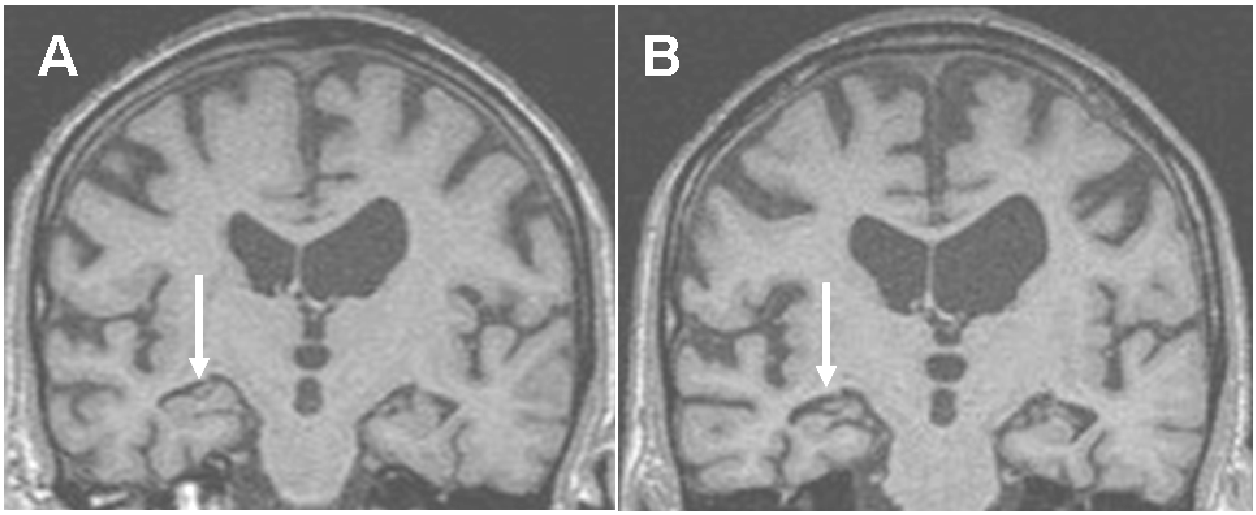
White matter lesions rating scale

WMH were rated using the Rotterdam Scan Study Rating Scale.[9] The rater was blinded to any clinical information of the patients. WMH were considered present if these were hyperintense on PD or FLAIR images without prominent hypo-intensity on T1 weighted images. WMH were assessed according to location in subcortical (SCWMH) and periventricular (PVWMH) regions using a previously described protocol.[9] In short: the number and size of SCWMH was rated on hard copy according to their largest diameter in categories of small (< 3 mm), medium (3 to 10 mm) or large lesions (> 10 mm). A total volume of SCWMH was calculated by considering them spherical as described previously.[9] PVWMH were rated semi-quantitatively per region: adjacent to frontal horns (frontal capping); adjacent to lateral wall of lateral ventricles (bands), and adjacent to occipital horns (occipital capping), on a scale ranging from 0 (no white matter lesions), 1 (pencil-thin periventricular lining), 2 (smooth halo or thick lining) to 3 (large confluent white matter lesions). The overall degree of PVWMH

was calculated by adding up the scores for the three separate regions (range 0-9). Intra-rater kappa's for PVWMH severity grades were between 0.6-0.8. The intra-rater intra-class-correlation coefficient for SCWMH rating was 0.95.

Medial temporal lobe atrophy

MTA was rated on a five-point scale (0-4) on a coronal T1 weighted image based on the width of the choroid fissure and the temporal horn and the height of the hippocampal formation.[10] The mean of the left and right MTA score was used in the analysis.
All MRI scans were rated by an experienced rater with good intra-rater reliability (kappa between 0.6 to 0.8).



Coronal slices at the level of the medial temporal lobe at baseline (A); MTA score = 2) and after a follow-up period of 3 years (B; MTA score = 4) in a 79 years old male AD patient with progression of MTA. Arrows indicate the right MTL.

Other covariates

Blood pressure was measured manually in a standardised manner by means of a sphygmomanometer with the patient in sitting position after 5 minutes of rest based on a single measurement. The first and the fourth Korotkoff sounds were used for the systolic and diastolic blood pressure, respectively. Hypertension was defined as a baseline systolic blood pressure ≥ 140 mm Hg and/or a baseline diastolic blood pressure ≥ 90 mm Hg and/or the baseline use of blood pressure lowering medication. Global cognitive function was assessed by the mini mental state examination (MMSE).[7]

Statistical analysis

Progression of both WMH and MTA was defined as an increase of 1 point or more on the rating scales between baseline and follow-up. The figure shows a typical example of MTA progression. We calculated the mean progression of MTA stratified on absence or presence of baseline and of progression of WMH by means of age and gender adjusted ANOVA. Odds ratios (OR) were calculated to quantify the association between baseline and progression of WMH (independent variable) and progression of MTA (dependent) by means of age and gender adjusted logistic regression analysis. Additional adjustments were made for the MMSE (as an indicator of dementia severity), systolic and diastolic blood pressure and the duration of follow-up. The relation between progression of WMH and progression of MTA may be confounded by the severity of baseline WMH since progression of WMH has shown to be significantly related to baseline presence of WMH,[11] also in patients with AD.[6] We therefore performed additional adjustments for baseline WMH in all analysis where progression of WMH was the independent variable.

Results

Patients with a follow-up scan were younger than those without (66.2 years (SD = 8.6) vs 72.3 years (SD = 9.5), $p < 0.05$). Roughly half of all patients were female, both in the group with as well as without a follow-up scan. Mean MMSE at baseline was 21.1 (SD = 5.2). Other baseline characteristics are presented in table 1. Except for age and MTA, there were no differences in baseline characteristics between those with or without follow-up MRI.

There were 25 patients (about 70%) who showed MTA progression. Patients < 70 years of age had a higher mean progression of MTA than those ≥ 70 years of age (0.7 (SD = 0.5) and 0.3 (SD = 0.5)), however this was not significant. There was no difference between men and women with respect to progression of MTA.

Progression of MTA was related to the presence of PVWMH at baseline and to progression of PVWMH. The mean MTA progression was 0.8 (SD = 0.5) and 0.3 (SD = 0.4) for patients with or without PVWMH at baseline ($p = 0.01$). Patients who showed progression of PVWMH over the course of their disease had a significantly higher progression of MTA than those without PVWMH progression (0.9 (SD = 0.4) and 0.4 (SD = 0.5), $p = 0.01$). This was not found for SCWMH (table 2).

Table 1. Characteristics of the study population at baseline, with or without serial MRI*.

Characteristic	With follow-up	Without follow-up	p-value
Number of subjects	35	252	
Age at baseline (years)	66.2 (8.6)	72.3 (9.5)	0.001
Women (%)	42.9	60.0	0.06
Mean duration of follow up (years; range)	2.2 (1.0-5.1)	n.a.	
Median MTA baseline (range)	1.5 (0-3.5)	2.0 (0-4)	0.048
Median MTA follow up (range)	2.0 (0-3.5)	n.a.	
Median delta MTA (range)	0.5 (-0.5-1.5)	n.a.	
Median PVWMH baseline (range)	1.0 (0-6)	1.0 (0-9)	0.98
Median PVWMH follow up (range)	2.0 (0-6)	n.a.	
Median delta PVWMH (range)	0.0 (0-3)	n.a.	
Median volume (ml.) SCWMH baseline (range)	0.04 (0-3.2)	0.03 (0-3.9)	0.70
Median volume (ml.) SCWMH follow up (range)	0.06 (0-3.9)	n.a.	
Median volume (ml.) delta SCWMH (range)	0.01 (-0.3 – 0.9)	n.a.	
Hypertension (%)	84.7	79.0	0.43
Systolic blood pressure (mm Hg)	151.9 (23.8)	152.1 (23.3)	0.92
Diastolic blood pressure (mm Hg)	84.1 (10.6)	85.7 (10.7)	0.34
MMSE	21.1 (5.2)	19.9 (5.4)	0.21

* Values are age and gender adjusted means (SD) or percentages. n.a.: not applicable.

Table 2. Mean progression of MTA by baseline and progression of WMH*.

	Baseline PVWMH		Progression PVWMH	
	absent	present	absent	Present
Mean MTA progression	0.3 (0.4)	0.8 (0.5)†	0.4 (0.5)	0.9 (0.4)†
	n = 17	n = 18	n = 9	N = 26

	Baseline SCWMH		Progression SCWMH	
	absent	present	absent	Present
Mean MTA progression	0.6 (0.5)	0.5 (0.5)	0.3 (0.4)	0.5 (0.4)
	n = 8	n = 27	n = 11	N = 24

* Means are adjusted for age, gender, duration of follow up and blood pressure; † p = 0.01

Patients with PVWMH at baseline had a 40-fold increased risk for progression of MTA compared to those without baseline PVWMH (OR = 40.0, 95% CI = 1.3 to $1.2x10^3$, p = 0.03). Patients with progression of PVWMH during the course of the disease had an increased risk for MTA progression (OR = 3.7 per degree increase of progression of PVWMH, 95% CI = 1.1 to 12.9; p = 0.04). There was higher risk for progression of MTA for those with progression of PVWMH than those without (OR = 10.9, 95% CI = 1.0 to 122.5, p = 0.05). This was not found for SCWMH (table 3).

Adjustment for confounding factors, including the degree of baseline WMH, did not alter the magnitude of the association.

Table 3. The relative risk for MTA progression in AD patients by baseline and progression of white matter lesions (OR and 95% confidence intervals).

	Periventricular WMH		Subcortical WMH	
	baseline*	progression†	Baseline*	progression†
Risk for progression of MTA	40.0 (1.3-$1.2x10^3$)‡	3.7 (1.1-12.9)¶	0.7 (0.1-5.2)	1.0 (0.99-1.02)

Adjustments were made for age, gender, duration of follow-up, systolic and diastolic blood pressure.
* The reference group consists of patients without WMH at baseline. † per unit of WMH progression.
‡ p = 0.03; ¶ p = 0.04

Discussion

We found that patients with WMH at baseline and those with an increase of WMH, especially the PVWMH, over a mean two-year period of follow-up had a significantly higher risk for progression of MTA.

Strengths of our study are the prospective nature of the study and the fact that baseline and follow-up scans were rated independently from each other with high intra-rater agreement.

Some methodological issues need attention. Selection bias may have influenced our findings in several ways. Due to the nature of a follow-up study only those participants that were still alive at follow-up, undergo serial MRI scanning. Therefore it could be that selective survival of people with a relatively mild degree of WMH at baseline and those with a relatively mild progression of WMH has occurred since severity of WMH is related to mortality.[12] Another form of selection bias may be the underrepresentation of those patients who are in a more advanced stage of the disease, and presumably have the highest degree of WMH, since those

patients are not very likely to show up at regular outpatient-clinic controls and at repeated MRI examination, for example due to mobility related problems.[13] However we do not think that these forms of bias significantly influenced our findings since in a previous study we found a linear relation between the degree of WMH and MTA, consequently those with the most severe WMH would most likely to have the most severe MTA.

WMH and MTA were rated with the Rotterdam scan study scale[9] and with a semi quantitative MTA rating scale respectively,[10] which both were not developed for the detection of change in a longitudinal design. The use of the Rotterdam scan study scale for this purpose proved to be poor in a recent validation study,[14] especially for the detection of change of PVWMH but performed better for the detection of change of SCWMH. A reason for this could be the so-called ceiling effect that presumably does not apply to the SCWMH. PVWMH that were already rated in the highest category at baseline (and which are most likely to progress) cannot contribute to progression on these scales since they are already in the highest category, whereas SCWMH were counted taking into account number and size of lesions without a predefined maximum, thus avoiding a ceiling effect. However the presumed influence of this ceiling effect is limited in our study since patients in our study had a median baseline PVWMH of 1.0 (which is way below the maximum of 9.0) compared to 6.0 in the study of Prins et al.[14]

This type of validation study has never been done for the detection of MTA change over time with the semi quantitative MTA rating scale we used but similar reasoning may apply, since mean MTA scores in our study were quite low and far below the maximum of the score.

Our finding of a relation between progression of WMH and progression of MTA could be confounded by baseline WMH since this has proven to be related to progression of WMH.[6,11] However, adjustment for baseline WMH did not alter the magnitude of the association rendering this explanation unlikely.

Our study does not provide an explanation on how WMH may ultimately lead to MTA in AD. An explanation could be that the medial temporal lobe is disconnected from connected cortical areas by the vascular WMH in the white matter tracts subserving the cortical association areas[15,16] leading to shrinkage of the medial temporal lobe due to Wallerian degeneration. Despite the fact that ours is a prospective study, both WMH and MTA were already present at baseline examination therefore causal inference on the underlying mechanism cannot be made from our study. It is not known why periventricular and subcortical WMH would have a differential influence on MTA. An explanation could be that the periventricular WMH affect areas of long fiber tracts that connect several distant cortical

areas with each other (including the MTA)[15,16] whereas subcortical WMH mainly disrupt short loops of cortico-cortical connections not related to distant structures such as the MTA.[17] Still, a remaining explanation for our finding includes the possibility of an identical underlying mechanism for both WMH and MTA such as changes in the amyloid metabolism or vascular brain disease. The predominant pathology in MTA even early in the course of AD is the presence of amyloid $_{\beta 1\text{-}42}$ in amyloid plaques.[18] Whereas recent studies also indicated a relation between the level of circulation $A_{\beta 1\text{-}42}$ and the presence of WMH.[19] Consequently, by these mechanisms progression of amyloid deposition could both lead to progression of both WMH and MTA, thereby explaining our finding. Another underlying mechanism may be that cerebral ischemia not only results in WMH but also in MTA. Indeed, pathological studies found micro-infarcts in the medial temporal lobe in patients with AD.[20]

Our findings suggest a relation between both baseline and progression of WMH and progression of MTA. When our findings are substantiated this may indicate that the presence of PVWMH on an MRI scan can be used as a tool that is able to predict MTA progression (and as such presumably progression of the disease) in still relatively mildly demented patients years before end stages of the disease. As such they may function as a surrogate end point in clinical trials that aim at modifying the course of AD.[21] If a causal relation between WMH and MTA progression is to be proven MTA progression may be prevented by modifying the progression of WMH by for example treatment of the vascular risk factors for WMH such as hypertension.[22]

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Chapter 6

Brain aging in very old men with type 2 diabetes mellitus: The Honolulu Asia Aging Study

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Abstract

Background

Type 2 Diabetes Mellitus (DM2) leads to cognitive impairment and dementia, which may reflect microvascular and macrovascular complications as well as neurodegenerative processes. There are few studies of the anatomical basis for loss of cognitive function in DM2.

Aim

To investigate the association between DM2 and markers of brain aging on magnetic resonance images (MRI), including infarcts, lacunes and white matter hyperintensities (WMH), as markers of vascular damage, and general and hippocampal atrophy (HA) as markers of neurodegeneration.

Setting

The Honolulu Asia Aging Study of Japanese American men born between 1900-1919 and followed since 1965.

Methods

Prevalent and incident dementia was assessed. Associations between MRI markers and diabetic status were estimated with logistic regression, controlling for socio-demographic and other vascular factors.

Results

The prevalence of DM2 in the cohort is 38%. Subjects with DM2 had a moderately elevated risk for lacunes (OR = 1.6, 95% CI = 1.0 - 2.6) and HA (OR = 1.7, 95% CI = 0.9 - 2.9). The risk for both HA and lacunes/infarcts was twice as high in subjects with, compared to those without DM2. Among the group with DM2, those with the longest duration, taking insulin, and with complications had relatively more pathologic brain changes.

Conclusions

There is evidence that older persons with DM2 have an elevated risk for vascular brain damage and neurodegeneration. These pathologies may be the anatomical basis for increased risk for cognitive impairment or dementia in DM2.

Introduction

Subjects with Type 2 Diabetes Mellitus (DM2) are at increased risk for cerebral complications, including stroke,[1,2] cognitive impairment[3,4] and dementia.[5-7] This may partially reflect the systemic microvascular (retinopathy, nephropathy, neuropathy)[8] and macrovascular (coronary heart disease, peripheral arterial disease)[9-11] complications that characterize DM2. Characteristics of subjects with DM2, such as hyperglycemia, elevated blood pressure, hyperinsulinemia and dyslipidemia, may also directly affect neuronal viability. In DM2, the phosphorylation of tau may be enhanced,[12] the breakdown of amyloid might be diminished,[13,14] and advanced glycated end products may contribute to the formation of neurofibrillary tangles (NFT) and neuritic plaques (NP),[15] which are markers of Alzheimer's disease (AD), a major neurodegenerative disease in the elderly. Autopsy data based on the Honolulu Asia Aging Study (HAAS) cohort show a significant association of DM2 to infarcts as well as hippocampal NFT and NP.[6]

Taken together, the evidence suggests that DM2 may contribute to cognitive disorders not only via vascular lesions, but also via neurodegeneration. To test this hypothesis, we investigated the association between DM2 and magnetic resonance image [MRI] findings of infarcts, lacunes and white matter hyperintensities (WMH), as markers of vascular damage, and general and hippocampal atrophy (HA)[16] as markers of neurodegeneration. Data are from the population-based Honolulu Asia Aging Study (HAAS).

Methods

The design of the HAAS has been described elsewhere.[17] Briefly, the cohort consisted of Japanese-American men born between 1900 and 1919, living on the Island of Oahu, Hawaii, who were enrolled in 1965 as a part of the Honolulu Heart Program (HHP). After the first exam (1965-1968), the men were re-examined in 1968 through 1970 (exam 2) and 1971 through 1974 (exam 3). In 1991 to 1993, the HAAS was established with the aim of investigating neurodegenerative diseases in the cohort. Of the survivors 3734 men (80% response) underwent a complete examination (exam 4). The cohort was re-examined 1994 to 1996 (exam 5), with an 84% participation rate among those with a previous cognitive screen. At each exam, clinical measures were made and socio-demographic and medical conditions assessed. At exam 4 and 5, cognitive status was tested and prevalent (exam 4) and incident (exam 5) dementia cases were identified. The Kuakini Medical Center Institutional Review

Board approved this study. All respondents signed informed consent forms, except those who were demented. In that case an informed caretaker signed the consent.

MRI sub-study

Sample

In exam 5, a MRI study was conducted on a sub-sample of the cohort selected on the basis of information from both exams 4 and 5.[18] The sample included a ~10% random sample of exam 5 participants, and a randomly selected over-sample of those with prevalent dementia (excluding the severely demented, who might not be able to undergo the procedure), those who scored poorly on the Cognitive Abilities Screening Instrument[19] but did not meet criteria for dementia, those with apolipoprotein E ε4 genotype, and those with clinical stroke.

Dementia was ascertained in a multi-step procedure, described in detail elsewhere.[17] Diagnosis was made in a consensus conference: DSM-IIIR criteria[20] were applied for dementia, NINDS-ADRDA[21] for AD, and the CADDTC for vascular dementia (VaD).[22] Stroke was identified from the first exam through to the MRI exam as a part of the ongoing HHP hospital surveillance system that uses multiple sources of information to complete a consensus diagnosis. Apolipoprotein E genotyping based on samples collected at exam 4 was performed with restriction isotyping using a polymerase chain reaction.[23]

Of the 845 men invited for the procedure, 621 MRI scans were acquired, and 543 MRI scans could be processed successfully for all relevant data. Non-participation was due to death, refusal and technical problems. Compared to the 302 subjects not included in the analyses, the included subjects had the same prevalence of DM2, hypertension and stroke, but had more frequently the apolipoprotein E ε4 allele (36 vs 29%, $p = 0.04$) and had more years of education ($p = 0.01$).

Imaging protocol

Scans were acquired with a GE Signa Advantage, 1.5 Tesla machine at Kuakini Medical Center, Honolulu. The acquisition protocol typically required 20 minutes and included four pulse sequences: sagital, 24 cm FOV, TR = 5000, TE = minimum, 5 mm contiguous interleaved sections, 192 views, 1 repetition; 3D coronal spoiled gradient echo sequence (SPGR), 22 cm FOV, minimum TR and TE, 1.6 mm slice thickness, 124 slices, 1 repetition, 45 degree flip angle; axial proton density weighted fast-spin echo sequence, 3 mm interleaved

sections, minimum TE, TR = 2300 msec, 24 cm FOV, 256 views, 1 repetition, 4 echo train length, minimum inter-echo spacing; another axial fast-spin echo sequence, T2-weighted, 3 mm interleaved sections, TR 4000 msec or more, 24 cm FOV, 256 views, 1 repetition, echo train length equal to 8, minimum inter-echo spacing.

MRI-readings

WMH, infarcts and lacunes: Semi-quantitative readings based on a protocol developed for the Cardiovascular Health Study were performed at the Johns Hopkins Neuroradiology Reading Centre by readers blinded to subject risk factors and health. Scans were evaluated for the number of lacunes and infarcts as defined by Longstreth.[24] In short, infarct or lacune are defined as a lesion at least 3 mm in diameter, visible on both the T1-weighted images and the PD/T2-weighted images and approach CSF-density. Infarcts in the cortical gray matter and basal ganglia may only be CSF-like on the T2/PD images. Lacunes are defined as exclusively located subcortically (including the basal ganglia) and are between 3 and 20 mm in all dimensions. Infarcts are larger than 20 mm or located cortically. WMH appear isointense compared to the white matter on the T1-weighted images and hyperintense on the axial PD-weighted images. They are rated on a 10-point scale that ranges from no white matter signal abnormalities to all white matter involved.[25]

Atrophy: The inner table distance and the bifrontal distance (largest diameter between the left and right frontal horn of the lateral ventricles) were measured on the most superior T1-weighted axial image where the lateral ventricles were indented by the thalami. The central sulcus width was the largest perpendicular diameter of the right central sulcus, also measured on the T1-weighted axial sequence. As a measure of cortical volume, the central sulcus width was divided by the inner table distance; cortical atrophy was defined as the highest quartile of this measure. As a measure of subcortical volume, the bifrontal distance was divided by the inner table distance; subcortical atrophy was defined as the lowest quartile of this measure. General atrophy was defined as the presence of cortical and/or subcortical atrophy.

Hippocampus volume: The coronal SPGR sequence was reformatted to oblique coronal, perpendicular to the long axis of the left hippocampus. Using MEDx version 3.41 software (Sensor Systems, Inc. Sterling, VA), one rater, blind to subjects characteristics, measured the left and right hippocampi as described in an earlier report.[26] The hippocampal formation, including the subiculum, dentate gyrus, cornu ammonis, fimbria and alveus, was measured in

its total length from anterior until the crux of the fornix was seen. The intra-class correlation coefficient for the intra-reader agreement was 0.97.

Hippocampal volumes were corrected for head size, estimated on the axial proton density sequence, by measuring the intra-dural area (total intracranial volume (TICV)). For each subject hippocampal volume was multiplied with the mean TICV of the sample and divided by the TICV of the subject.[26]

Assessment of DM2

DM2 was assessed at the fourth exam. Subjects with a self-reported doctor's diagnose of DM2, use of oral hypoglycaemic medications or insulin are classified as DM2. To identify other individuals with glucose dysregulation, we obtained fasting and 2-hr glucose levels on those who were not known to have DM2, and did not have a gastrectomy, active peptic ulcer, or stomach cancer, by administering a 75g-glucose drink.[27] Based on the recommendations of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus[28] individuals with fasting blood glucose $\geq$ 126 mg/dl ($\geq$ 7.0 mmol/l) or a 2-h post load glucose $\geq$ 200 mg/dl ($\geq$ 11.1 mmol/l) were classified as having DM2; individuals with a fasting glucose between 5.1 and 7.0 mmol/l or a 2-hour post load glucose between 7.8 and 11.1 mmol/l were classified as glucose intolerant (IGT); subjects with a fasting glucose $\leq$ 5.1 mmol/l and a 2-hour post load glucose $\leq$ 7.8 mmol/l were classified as normoglycemic (NG). Subjects reporting DM (not those newly detected by the study) were asked the duration of their disease, and whether they suffered from complications of DM2, including amputation, retinopathy, nephropathy, or peripheral neuropathy.

Measures of confounding or mediating variables

We considered the following factors to be possible confounders or mediators of the association between DM2 and MRI-measurements: age, education (years), history of coronary heart disease (CHD), ankle-brachial index (ABI), mid-life smoking (never (reference), current and past), systolic blood pressure (SBP), body mass index (BMI) and total cholesterol, as well as treatment with anti-hypertensive medication. CHD history was assessed at baseline in 1965 and throughout the entire follow-up to the MRI exam. ABI was measured at exam 4. Smoking was collected by questionnaire at the mid-life exams (exam 1, 2 and 3). The values of BMI (kg/m2), total cholesterol (mg/dl) and SBP (mmHg) are the average of these factors measured

at the three mid-life exams Treatment with anti-hypertensive medication was based on self-report (exam 1-3) or by presentation of medication vials (exam 4).

Statistical analyses

Age-adjusted differences in subject characteristics were examined across diabetic subgroups using analyses of variance if the characteristic was continuously distributed and with Mantel-Haenszel test if it was categorical.

Logistic regression was used to estimate the association of the three glycemic categories (DM2, IGT and NG) to brain outcomes. For the analyses we defined the brain outcomes as follows: lacunes (present/absent), infarcts (present/absent), substantial WMH (score 4 and higher versus the rest), severe HA (the lowest 25^{th} percentile of hippocampal volume versus the rest) and general atrophy. To examine the simultaneous risk for both vascular damage and HA, we created a polytomous four-level outcome: only HA, only infarcts or lacunes; both HA and lacunes/infarcts. The reference group had no infarcts, lacunes or HA.

Three models were estimated: model 1, adjusted for age and education; model 2 also adjusted for MRI variables other than the lesion of interest; and model 3 adjusted for apolipoprotein E genotype, dementia status, smoking, alcohol use, history of CHD and stroke, SBP, anti-hypertensive drug use, cholesterol, BMI and ABI. We also conducted sub-analyses to investigate whether subjects with presumably more severe or long-standing DM2 were at higher risk for the MRI outcomes. Markers of disease history included whether insulin is used, duration of disease and self reported presence of DM-related amputation, eye, kidney or peripheral neuropathic complications. Analyses were conducted with the Statistical Analysis System [v. 8]; the analyses with the polytomous outcome were conducted with STATA.[29]

Results

In the sample, 38% had DM2 (65% of whom had known diabetes), 25% had IGT and 37% were NG (table 1). The mean age of the men was 81.6 years (SD = 5.0). Proportionately more subjects with DM2 used anti-hypertensive drugs, had CHD, smaller hippocampi, and more lacunes ($p < 0.05$, age adjusted). Insulin levels, and by definition, fasting glucose levels were higher in subjects with DM2 or IGT ($p < 0.001$ and $p < 0.05$, respectively) compared to NG.

Table 1: Characteristics of the MRI sample by diabetes status: the HAAS

Variable	No diabetes	IGT	DM2
N	204	137	202
Age (years (SD))	81.3 (4.9)	81.8 (5.0)	81.7 (5.1)
Education (years (SD))	10.2 (3.3)	10.4 (2.8)	10.3 (3.2)
SBP (mmHg (SD))	131 (16)	133 (18)	134 (17)
DBP (mmHg (SD))	83 (9)	83 (9)	83 (10)
BMI (kg/m^2 (SD))	23.5 (2.7)	23.5 (2.2)	24.3 (2.7)
Antihypertensives (%) *	41	47	55
Total cholesterol (mg/dl (SD))	215 (31)	220 (30)	222 (32)
Fasting glucose (mg/dl (SD)) †	98 (6)	107 (8)	132 (37)
Fasting insulin (μIU/ml (SD))*	12.6 (9.3)	14.0 (7.4)	18.6 (15.8)
Smoking (%)			
Former	34.3	31.4	55
Current	25.0	19.0	2.5
Apo E ε4 (%)	36.8	38.0	35.1
ABI (SD)	1.04 (0.15)	1.04 (0.15)	1.03 (0.19)
CHD (%)*	12.3	10.2	18.3
Stroke (%)	6.9	11.7	9.4
Dementia (%)	21	20	22
AD	9.8	8.8	8.9
AD w/ CVD	2.5	5.1	5.4
VaD	2.9	3.6	5.4
Hippocampal volume (mm^3 (SD)) *	5406 (856)	5430 (855)	5348 (805)
Hippocampal atrophy (%)	22	23	27
Lacunes (%)*			
0	61.8	61.3	47.5
1	19.6	16.1	24.8
$\geq$2	18.6	22.6	27.8
White Mater Hyperintensities (%)			
0-3	73.5	69.3	74.8
4-9	26.5	30.7	25.2
Infarcts (%)	9.8	13.0	13.4
General atrophy (%)	41.1	41.6	46.0

p-values adjusted for age. *p<0.05; †p<0.001. Smoking: 30 missing subjects.
Apo E ε4 groups includes 15 subjects with ε 24.

Table 2: Association between diabetes mellitus and MRI-outcome variables: the HAAS.

	Model 1	**Model 2**	**Model 3**
General atrophy			
NG	1	1	1
IGT	1 (0.6-1.5)	1 (0.6-1.5)	1 (0.6-1.6)
DM2	1.2 (0.8-1.8)	1.2 (0.8-1.7)	1.1 (0.7-1.7)
WMH			
NG	1	1	1
IGT	1.2 (0.7-1.9)	1.2 (0.7-1.9)	1.3 (0.8-2.3)
DM2	0.9 (0.6-1.4)	0.9 (0.6-1.4)	1.1 (0.7-1.9)
Infarcts			
NG	1	1	1
IGT	1.4 (0.7-2.9)	1.6 (0.8-3.1)	1.0 (0.4-2.7)
DM2	1.5 (0.8-2.7)	1.5 (0.8-2.8)	1.9 (0.8-4.3)
Lacunes			
NG	1	1	1
IGT	1.0 (0.6-1.6)	1.0 (0.6-1.6)	0.9 (0.6-1.6)
DM2	1.8 (1.2-2.6)	1.8 (1.2-2.6)	1.6 (1.0-2.6)
Hippocampal atrophy			
NG	1	1	1
IGT	1.0 (0.6-1.8)	1.0 (0.6-1.7)	1.2 (0.7-2.3)
DM2	1.3 (0.8-2)	1.3 (0.8-2.1)	1.7 (0.9-2.9)

Model 1: adjusting for age and education.
Model 2: as model 1, for atrophy and hippocampal atrophy also adjusting for WMH, infarcts and lacunes; for WMH, infarcts and lacunes also adjusting for general atrophy.
Model 3: as model 1, also adjusting for Apo E genotype, dementia, smoking, alcohol, CHD, ABI, systolic blood pressure, blood pressure treatment, BMI, total cholesterol and stroke.
General atrophy = cortical atrophy (the highest quartile of the width of central sulcus/ inner table distance) and/or subcortical atrophy (the lowest quartile of the bifrontal distance/ inner table distance); WMH = wml score $\geq$ 4; infarcts = cortical infarcts (any cortical infarcts) and/or subcortical infarcts (any subcortical infarcts); lacunes = any lacunes; hippocampal atrophy = lowest quartile of the hippocampal volumes.

Compared to NG men, those with DM2 had a raised risk for lacunes (OR = 1.6, 95% CI = 1.0- 2.6) (table 2). Subjects with DM2 similar risk for general atrophy as did the NG group. In the fully adjusted model 3, the risk for HA was moderately higher for DM2 subjects compared to NG subjects (OR = 1.7, 95% CI = 0.9- 2.9). Subjects with IGT had essentially the same risk as the NG subjects for all investigated MRI outcomes (table 2).

The combined groups based on presence or absence of vascular lesions and HA (table 3) suggest that those with DM2 have an two times increased risk for a mixed pathology of vascular lesions and HA. However, the risk in the mixed profile group is similar to what would be expected if DM2 increased the risk for the two types of pathology in an additive manner. Compared to the NG, the IGT did not have a significantly higher risk for these outcomes.

Table 3: Association of diabetes mellitus, hippocampus and lacunes/infarcts: the HAAS

	Model 1	**Model 3**
Hippocampal atrophy only		
IGT	1.4 (0.7-2.7)	1.5 (0.7-3.1)
DM	1.5 (0.8-2.7)	1.7 (0.8-3.4)
Lacunes/infarcts only		
IGT	1.2 (0.7-2.0)	1.2 (0.7-2.1)
DM	1.9 (1.2-3.0)	1.8 (1.1-2.9)
Hippocampal atrophy and lacunes/infarcts		
IGT	0.9 (0.0.4-2.0)	0.9 (0.4-2.30
DM	2.1 (1.1-4.11)	2.0 (0.9-4.4)

Model 1: adjusting for age and education
Model 3: as model 1, also adjusting for Apo E genotype, dementia, smoking, CHD, ABI, systolic blood pressure, blood pressure treatment and BMI.
Hippocampal atrophy = lowest quartile of the hippocampal volumes without lacunes or infarcts; lacunes/infarcts = any lacunes or infarcts without hippocampal atrophy; hippocampal atrophy and lacunes/infarcts = lowest quartile of the hippocampal volumes with lacunes or infarcts.

Only 10 subjects with DM2 (5% of DM2) used insulin. The mean hippocampal volume of these subjects was smaller than those subjects with DM2 who did not take any medications (4778 mm3 (SD 825) vs 5400 (SD 833) mm3 respectively), they had more frequently general

atrophy (70% vs 42.7%); 40% had hippocampal volumes in the lowest quartile, and 50% had lacunes. Three of the ten were demented. There were 49 subjects with DM2 (24.2%) who used oral hypoglycaemic drugs. The average hippocampal volume of these subjects was 5312 (SD 818) mm3, 29% had small hippocampi, 59 % had lacunes and 9 were demented.

Twelve subjects reported DM2-related complications. Compared to subjects with DM2 without, those with complications had slightly more brain atrophy (59% vs 50%) and infarcts (25% vs 10%), but the sample is very small. Compared to the subjects with DM2 $\leq$ 5 years (n = 53), those with DM2 for more than 20 years (n = 25) had more lacunes (68% v 54.7%), hippocampal atrophy (44% vs 28.3%), infarcts (20% vs 15%), and WMH (36% vs 20.7%).

Discussion

Subjects with DM2 had an elevated risk for lacunar infarction, and a borderline significantly raised risk for HA. The risk for both infarcts and HA was twice as high in the subjects with DM2 compared to subjects without DM2 after adjusting for other vascular factors. This risk estimate suggests there is no synergism between the two pathologies. Compared to NG, subjects with IGT, who are at high risk of developing DM2, had no elevated risk for general atrophy, lacunes, infarcts or HA. These associations were independent of other vascular outcome measures and risk factors, and also independent of each other.

This study had several strengths. It is based on a large sample of subjects with MRI of the brain, and cardiovascular data that were collected prospectively from mid-life up through late-life when the MRI was acquired. Also, we separated the subjects with IGT, who are at risk for DM2, from the subjects with IGT and DM2, so groups with different degrees of glucose regulation could be compared. The finding of very small hippocampi in insulin users, and proportionately more brain pathology in those who have been DM2 at least 20 years, suggest that the amount of brain pathology may increase with disease severity or duration. However this needs to be further investigated in a larger sample that is prospectively followed.

When generalizing the results to other reports, some characteristics of the sample should be noted. It has been reported that the prevalence of DM2 and glucose dysregulation in this cohort is comparatively high, and that this may reflect differences in the relative contributions to the disease of insulin resistance, glucose over-production, degree of impaired ß-cell function, and genetics.[30] Such differences may also account for the relatively low use of insulin and complications in this diabetic population. Other differences that might modify these results include the fact these men are relatively lean, and the mean age in the cohort is

high [>80 yrs]. It is likely that many subjects with DM2, who have severe complications of the disease, do not reach this age. If mortality is selective for men at risk for DM2 and cerebrovascular changes, this would change the estimates of the associations reported here. In this context, the risk estimates we found are of moderate size. It should also be noted that the MRI sample is not a random sample of the cohort but a sample selected based on certain characteristics including dementia, poor cognitive performance, stroke and Apolipoprotein E genotype.

DM2 leads to both microvascular and macrovascular changes. Atherosclerosis of the large extra- and intracranial vessels, decreased cerebral blood flow, impaired cerebrovascular reactivity, thickening of the capillary basement membrane and endothelial cell degeneration of microvessels are all described in DM2 (for review, see 31). We found associations between DM2 and lacunes, which is a marker for microvascular or small vessel disease. In another community-based study, subjects with DM2 also had a higher risk for lacunes compared to NG.[25] A study with serial MRI-scans also detected more new lacunes in the subjects with DM2.[32] The idea that DM2 leads to small vessel disease in the brain is supported by these studies. However, WMH is also considered to be small vessel disease but we did not find an association between those lesions and DM2. This might be due to the scoring system that was used. Although, as expected, the score is significantly associated with age, clinically silent stroke, higher systolic blood pressure and impaired cognition,[33] it does not evaluate the distribution of the lesions, or provide a quantitative measure of lesion load. Further, we did not acquire a fluid attenuated inversion recovery sequence, so WMH may have been missed.[34-36] However, the lack of association between DM2 and WMH has also been reported in other studies,[37,38] in which a semi-quantitative method for estimating the WMH volume has been used. These findings suggest that, in DM2, WMH may have a different pathologic basis than lacunes, but this needs to be further investigated.

Cortical and subcortical infarcts are caused by macrovascular or large vessel disease. We did not find a significant association between DM2 and infarcts, although risk ratios were raised. This is consistent with reports from other studies.[37,38] This is a notable finding, as DM2 is a risk-factor for stroke.[2,39] The difference may be related to selective mortality of subjects with DM2 at risk for macro-vascular disease.

Hippocampal atrophy is a general marker for neurodegenerative processes, particularly in AD.[16] Cerebral hypoxia-ischemic conditions can also lead to cell death and ensuing hippocampal atrophy.[26,37] Subjects with DM2 are also at moderately increased risk for HA, particularly when infarcts and lacunes are also present. Adjusting for vascular risk factors

(model 3) slightly attenuated the odds ratio, suggesting some mediation by these factors. This is consistent with the findings in the HAAS autopsy study, which showed both amyloid related pathology and vascular pathology were more frequent in DM2 compared to the rest of the sample.[6] In the present study, DM2 was not associated with general atrophy. The large community-based study CASCADE did find that DM2 was associated with an increased risk for cortical atrophy,[38] particularly in those with hypertension. These subjects were much younger than those in the HAAS.

There are several mechanisms that can explain the influence of DM2 on neurodegeneration. Insulin has an inhibitive effect on the phosphorylation of tau. Tau is a phosphoprotein of the brain, and normally has 2 or 3 phosphate groups. Hyperphosphorylation of tau can lead to NFT, what is a characteristic of AD. As DM2 is characterized by signalling defects in insulin the inhibitive effect of insulin on phosphorylation of tau[12] may be diminished. Dysfunction of the insulin degrading enzyme (IDE) may also be a possible pathologic link between AD and DM2. This enzyme is known to degrade insulin and β-amyloid. In DM2, dysfunction of IDE causes high levels of insulin and β-amyloid. Deposition of β-amyloid into NP is characteristic of AD. In AD, hyperinsulinemia is more prevalent compared to controls, and the activity and amount of IDE is diminished.[40,41] Interestingly, chromosome 10 contains the genes for IDE, and potentially genes for both late onset AD and DM2.[13,14,42] Another possible neurodegenerative mechanism is through the neurotoxic advanced glycation end products, caused by hyperglycemia, which may contribute to the formation of NFT and NP.[15,43]

We did not find an increased risk for MRI detected brain changes in men who had IGT. There are data based on 30 subjects without DM2[44] suggesting that fasting and 2-hour glucose levels were negatively associated with hippocampal volume. However, studies based on larger, less selected samples, are contradictory regarding the risk for cognitive impairment in those with IGT.[45,46] Given the high prevalence of IGT it will be important to further investigate this group in studies of brain aging.

In summary, we found that subjects with DM2 had a moderately elevated risk for vascular brain damage, such as lacunes, and for neurodegeneration, such as is indicated by HA. Due to advances in treatment, subjects with DM2 are living longer. However, the pathology may cause cognitive impairment and subsequent difficulties in disease management. Further studies on the changes in brain structure and correlation with cognition in DM2 are warranted.

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Chapter 7

Diabetes mellitus, hypertension and medial temporal lobe atrophy: the LADIS study.

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Diabetic Medicine, in press

Abstract

Hypothesis

Based on recent findings on the association between vascular risk factors and hippocampal atrophy, we hypothesized that hypertension and diabetes mellitus (DM) are associated with medial temporal lobe atrophy (MTA) in a sample with non-disabled subjects, independent of the severity of white matter hyperintensities (WMH).

Methods

In the Leukoaraiosis And DISability in the elderly (LADIS) study, we investigated the relation between DM, hypertension, blood pressure and MTA in 582 subjects, stratified by WMH severity, using multinomial logistic regression. MTA was visually scored for the left and right medial temporal lobe (score 0 to 4), and averaged.

Results

Mean age was 73.5 year (SD 5.1), 54% was female. Of the subjects, 15% had DM, and 70% had a history of hypertension. Subjects with DM had a significantly raised odds for MTA score 3 (OR = 2.9; 95% CI = 1.1 – 7.8), and a modestly increased odds for MTA score 2 (OR = 1.8; CI = 0.9 – 4) compared to a MTA score of 0 (no atrophy). Systolic and diastolic blood pressure and a history of hypertension were not associated with MTA. There was no interaction between DM and hypertension. Stratification on WMH did not alter the associations.

Conclusion

Our study strengthens the observation that MTA is associated with DM, which is independent of the amount of small vessel disease as reflected by WMH.

Introduction

Structures in the medial temporal lobe have a crucial role in memory function. Medial temporal lobe atrophy (MTA) is classically thought to be a result of neurodegeneration with deposition of neurofibrillary tangles and neuritic plaques,[1,2] especially in Alzheimer's disease (AD). However, new findings from two longitudinal population-based studies and a study among patients with AD indicate that vascular factors including diabetes mellitus (DM) and hypertension may also play a role in MTA.[3-5] It is unclear how these factors can lead to MTA. There could be a direct effect of the vascular factors resulting in microvascular, metabolic-toxic or other changes in the medial temporal lobe, which ultimately could result in MTA. Alternatively, WMH may be an intermediate in this process: vascular factors cause WMH, which in turn may attribute to MTA, possibly by Wallerian degeneration.[6,7]

We therefore investigated the association between DM, hypertension and MTA, stratified on the severity of WMH in a large group of independently living elderly.

Methods

The Leukoaraiosis And DISability in the elderly (LADIS) study[8] was designed to study the influence of WMH on transition to disability, morbidity, mortality and on the quality of life. The study is based on a multicenter and multinational collection and follow-up of initially non-disabled elderly subjects between 65 and 84 years of age, who were enrolled in 11 European centers. In order to be included the subjects had to be non-disabled, defined as no impairment at all or only one item compromised on the Instrumental Activities of Daily Living scale [9], and the MRI had to show some degree of WMH, stratified on the 3 severity classes of a revised version of the Fazekas WMH scale.[10] Subjects were excluded if they had severe illnesses (cardiac, hepatic, or renal failure, cancer or other relevant systemic diseases), severe unrelated neurological diseases, leukoencephalopathy of non-vascular origin (immunologic-demyelinating, metabolic, toxic, infectious, other), severe psychiatric disorders, inability to give an informed consent, or inability or refusal to undergo cerebral MRI. For a full description of the sample, we refer to Pantoni et al.[8]

At baseline, social background and medical history were assessed through a structured interview. A physical exam was performed by a physician. Subjects are currently followed-up for 3 years with repeated clinical and MRI studies. The present paper is based on the baseline data of the LADIS project.

Vascular risk factors

The history of hypertension, previously assessed by a physician, was collected and reviewed during the interview with the aid of a structured questionnaire, and had to be based on multiple blood pressure measurements, taken on several separate occasions according to the World Health Organization Guidelines for the management of hypertension.[22] In these guidelines, hypertension is defined as a systolic blood pressure (SBP) of 140 mmHg or greater and/or a diastolic blood pressure (DBP) of 90 mmHg or greater in subjects who are not taking antihypertensive medication. Also, subjects using antihypertensive medication were labeled as hypertensive. If necessary, the family doctor was contacted. In addition to the diagnosis of hypertension, the blood pressure was measured once in supine position during the baseline examination.

A history of DM as previously assessed by a physician was based on the internationally accepted criteria for DM. These are a 8-hour fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) with symptoms of DM, or two measurements of fasting plasma glucose ≥ 7.0 mmol/L.[23] In addition, a random venous glucose (mmol/l) was measured at the baseline examination. Current use of drugs for hypertension (beta-blockers, Ca-antagonisten, ACE inhibitors, Alpha2-agonist, angiotensin-antagonist, diuretics, nitrates) and DM were registered in a structured way.

MRI

All subjects were studied by MRI following a standard protocol. MRI scans were made on a 0.5T (one center) or 1.5T scanner (ten centers) and included at least axial T2-weighted images, fluid attenuated inversion recovery (FLAIR) images and a coronal or sagittal T1-weighted 3D MPRAGE (magnetization prepared rapid acquisition gradient echo) sequence. All scans were transferred to the Image Analysis Center (IAC) in Amsterdam, the Netherlands, for central data storage. WMH severity was determined on the FLAIR sequence using the Fazekas scale:[10] the scale includes score 1 (mild: single lesions below 10 mm; areas of "grouped" lesions smaller than 20 mm in any diameter), 2 (moderate: single lesions between 10 to 20 mm; areas of "grouped" lesions more than 20 mm in any diameter; no more than "connecting bridges" between individual lesions) and 3 (severe: single lesions or confluent areas of hyperintensity 20 mm or more in any diameter). The sagittal MPRAGE

sequences were reformatted to coronal. Medial temporal lobe atrophy was assessed on the coronal T1 weighted sequences using the MTA-scale.[24] The MTA-scale ranged from 0 to 4: 0 = no atrophy; 1 = widening of the choroid fissure; 2 = widening of the choroid fissure and the temporal horn; 3 = widening of the choroid fissure and temporal horn and diminishing height of the hippocampus; 4 = severe atrophy. The mean of the left and right MTA was used in the data-analyses. In clinical practice, a score of 0 and 1 is interpreted as normal, and a score of 2-4 is indicative of atrophy. To determine the intra-rater reliability, 18 scans were scored twice for WMH and 15 scans for MTA (weighted Cohen's kappa for WMH = 0.84 and for MTA = 0.85).

Statistics

In the LADIS, a total of 639 subjects were included. Of 56 subjects, the quality of the MPRAGE-sequence was insufficient to be read for MTA. Information on vascular factors was not available for 1 subject. Therefore 582 subjects were included in the present study.

Differences between MTA-groups were assessed using analyses of variance for continuous data, and chi-square testing for categorical data.

The relation between blood pressure, hypertension, DM, venous glucose and MTA was investigated by multinomial logistic regression. MTA was the dependent variable, with MTA = 0 as reference group. Separate models were run for SBP, DBP, hypertension and DM. Adjustments were made for age, sex and education (years), as these variables were significantly associated with both outcome and risk factors. Data were presented as odds ratio's with accompanying 95% confidence interval (OR (95% CI)) for the 4 MTA-groups. The interaction of blood pressure treatment and SBP and DBP was tested with their interaction terms in the regression models. Also, the interaction between DM and hypertension was tested by their interaction terms in the regression models. To test the possible mediating effect of WMH, all models were then run stratified by WMH-severity.

Table 1: Demographic Data: The LADIS-Cohort.

Variable	MTA 0 (n = 126)	MTA 1 (n = 287)	MTA 2 (n = 123)	MTA 3 (n = 40)	MTA 4 (n = 6)
Age (years, mean (SD))*	72.5 (4.8)	74 (5.1)	75.3 (4.7)	76.3 (4.7)	75.4 (4.8)
Gender (n (%) female)	77 (61.1)	160 (55.7)	59 (48)	11 (36.7)	3 (50)
Education (years, mean (SD))	9.8 (4)	9.9 (4.0)	9.2 (3.4)	8.9 (3.7)	7.5 (1.6)
BP-treatment (n (%))	67 (53.2)	180 (62.7)	79 (64.2)	23 (57.5)	2 (33.3%)
Cerebrovascular accidents (n (%))	26 (20.6)	84 (29.3)	40 (32.5)	14 (35)	3 (50)
WMH-score (n (%))*					
mild	84 (66.7)	128 (44.6)	30 (24.5)	14 (35)	1 (16.7)
moderate	28 (22.2)	103 (35.9)	46 (37.4)	6 (15)	1 (16.7)
severe	14 (11.1)	56 (19.5)	47 (38.2)	20 (50)	4 (66.7)

Demographic data of LADIS patients included in this study.
WMH-score according to the WMH scale of Fazekas; MTA = medial temporal lobe atrophy.
BP-treatment: number of subjects treated for high blood pressure with anti-hypertensive medication (beta-blockers, Ca-antagonisten, ACE inhibitors, Alpha2-agonist, angiotensin-antagonist, diuretics, nitrates).
* $p < 0.001$

Results

Mean age was 73.5 year (SD = 5.1year), 54% was female. Of the subjects, 15% had DM, and 70% had hypertension. Of those with DM, 10 were treated with insulin (of which 7 also used oral anti-diabetic drugs), 37 with only oral anti-diabetic drugs, and 37 were not treated with medication. Subject with DM had similar WMH severity compared to the subjects without DM ($p = 0.4$).

Subjects with a higher MTA score were older ($p < 0.001$) and had more WMH ($p < 0.001$) (table 1). There was no association between MTA and sex, education, BP treatment or prevalence of cerebrovascular accidents.

DM was associated with MTA (table 2): subjects with DM had a modestly increased odds for MTA score 2 (OR 1.8; CI: 0.9 – 4), and a significantly raised odds for MTA score 3 (OR = 2.9; 95% CI = 1.1 – 7.8) compared to a MTA score of 0 (no atrophy). No subjects with DM had a MTA score of 4. Mean severity of MTA in those treated with insulin, with oral anti-diabetics and those who were untreated was similar. Stratification on WMH did no show a different result, although significance was lost due to small sample size (data not shown). There was no significant association between venous glucose and MTA.

Table 2: The Association Between Blood Pressure, DM and MTA:

multinomial logistic regression (n = 582).

Variable		MTA 0 (n = 126)	MTA 1 (n = 287)	MTA 2 (n = 123)	MTA 3 (n = 40)	MTA 4 (n = 6)
DM	n (%)	13 (10.3)	42 (14.7)	20 (16.5)	9 (23.1)	0
	OR (95% CI)	1 (ref)	1.5 (0.8-3.0)	1.8 (0.9 – 4)	2.9 (1.1 – 7.8)	-
Glucose (mmol/l)	mean (SD)	5.7 (1.6)	5.8 (1.8)	6.1 (1.8)	5.9 (1.7)	5.6 (0.7)
	OR (95% CI)	1 (ref)	1.0 (0.0-1.2)	1.1 (1-1.3)	1.1 (0.9-1.4)	1 (0.5-2.0)
Hypertension	n (%)	83 (65.9)	200 (69.9)	90 (73.2)	27 (67.5)	5 (83.3)
	OR (95% CI)	1 (ref)	1.3 (0.8–2.0)	1.6 (0.9-2.7)	1.2 (0.6-2.7)	2.6 (0.3-24)
SBP (mmHg)	mean (SD)	149 (22)	149 (20)	148 (21)	149 (20)	151 (10)
	OR (95% CI) per 10 mmHg	1 (ref)	1.0 (0.9-1.1)	1 (0.9-1.1)	1.0 (0.8-1.2)	1.0 (0.7-1.6)
DBP (mmHg)	mean (SD)	83 (11)	85 (11)	82 (11)	82 (9)	85 (8)
	OR (95% CI) per 10 mmHg	1 (ref)	1.2 (0.97-1.5)	0.9 (0.7-1.2)	1.0 (0.7-1.5)	1.2 (0.6-2.6)

Multinomial logistic regression for the printed variables, with MTA as dependent variable, with MTA 0 as reference score. Presented are the OR (95%CI). All models are adjusted for age, sex and education. Separate models for separate variables.
DM = diabetes mellitus; SBP = systolic blood pressure; DBP = diastolic blood pressure; MTA = medial temporal lobe atrophy.

SBP and DBP were not associated with MTA (table 2) in the total sample, nor in the subsample of subjects with a history of hypertension, nor in the subsample of subjects without a history of hypertension (data not shown). Subjects with hypertension had no increased odds for MTA (table 2). Stratification on WMH did not alter the associations importantly. There was no interaction with anti-hypertensive treatment. No significant interaction of hypertension and DM was found.

Discussion

In the present study we found that subjects with DM have a higher risk for MTA compared to subjects without DM. Subjects with hypertension did not have an increased risk for MTA. The degree of WMH did not modify the results.

The LADIS study provides a good sample to investigate the influence of vascular factors on MTA for several reasons. Principally it consists of non-disabled subjects, who consequently have no or only mild cognitive deficits. Therefore, the blood pressure lowering effect of dementia[25,26] does not come into play. Also, data on treatment of hypertension, age, sex, education and DM are collected in a standardised way. In addition, the study was set up to include a wide range in severity of WMH among the subjects, so the modifying effect of WMH in the association of vascular risk factors and MTA can be studied.

On the other hand, however, the included subjects do not represent the normal population, but are a selection of subjects who were referred to a clinic for several reasons. To be included in the LADIS, subjects had to be non- or only mildly disabled. Subjects with severe MTA, who are likely to have cognitive defects, were therefore unlikely to be included in the study. This is reflected in the fact that 71% of the subjects had no appreciable MTA (score 0 or 1), and only 8% had severe MTA (score 3 or 4). Furthermore, because only data from the baseline assessment were used in the present study, no effect changes over time could be taken into account.

In the Honolulu Asia Aging study[4] and in the Rotterdam study,[3] both population based longitudinal studies, untreated diastolic hypertension in midlife was associated with hippocampal atrophy in late life. Correction for WMH did not change this association. In subjects with AD, an association was found between systolic blood pressure and MTA, especially in subjects with WMH. This study was cross-sectional, and the effect was small, but significant.[27] Increased blood pressure is associated with more neurofibrillary tangles and neuritic plaques in the hippocampus.[28,29] Increased blood pressure could also lead to an impaired cerebral blood flow and subsequently damage the hippocampus, especially in the ischemia-sensitive CA1 area.[30-32] These influences could lead to MTA. Our negative observation in this respect is probably caused by sample characteristics: the limitation of subject inclusion to non-disabled subjects has inevitably resulted in little variation in MTA. Furthermore, it is conceivable that baseline hypertension predicts MTA at follow up.[3,4]

Our findings of an association between DM and MTA are in agreement with the Rotterdam study[5] that reported the volume of the hippocampus to be significantly smaller in subjects

with DM, independent of other vascular risk factors. There are several mechanisms that can explain the influence of DM on MTA. One of them is through insulin. As in non-insulin dependent DM insulin has signalling defects, the inhibitive effect of insulin on phosphorylation of tau[33] may be diminished. Also, with high insulin levels, insulin degrading enzyme will be inhibited to break down amyloid beta.[34,35] Another possible mechanism is through advanced glycated end products, that is caused by hyperglycemia and may contribute to the formation of neurofibrillary tangles and neuritic plaques.[36] These processes are known to be present in AD, in which disease the medial temporal lobe is primarily affected. However, the evidence that DM is importantly associated with MTA is not extensive, and the present data are not unambiguously interpretable, as the effect size is small and the number of subjects with anti-hyperglycaemic treatment is not large.

Earlier studies have shown an additive effect of DM and hypertension on vascular morbidity and mortality,[37] including stroke. In the CASCADE study,[38] subjects with DM and hypertension had an increased risk for cortical atrophy. Other studies have shown an additive effect of DM and hypertension on poor or decline of cognitive function.[39,40] These studies all suggest that in the presence of both risk-factors the risk of brain damage is higher. Although this hypothesis is plausible, our data do not support this, as there was no interaction between DM and hypertension.

The severity of WMH did not influence the association between hypertension, DM and MTA. WMH can be a result of hypertension.[41-43] In theory, WMH can interrupt neuronal tracts projecting from the cortex to the entorhinal cortex and hippocampus, both part of the medial temporal lobe. This could cause Wallerian degeneration and subsequently MTA, as was suggested in earlier reports.[6,7] Our data are not consistent with this theory.

In conclusion, our study strengthens the observation that MTA is associated with DM, independently of the amount of small vessel disease as reflected by WMH. Future research should explore the pathological mechanisms more in detail and the influence of strict regulation of glucose on the hippocampal volume.

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Chapter 8

Summary and general discussion

This thesis was written to basically explore two questions:

- Is hippocampal atrophy a good predictor for dementia in subjects with MCI?
- What are risk factors for hippocampal atrophy?

Chapter 2

The first question was addressed in chapter 2. 75 subjects with MCI who visited an outpatient clinic, underwent MRI as part of the routine clinical examination. After a mean follow-up of 34 months, 49% were considered demented. The medial temporal lobe atrophy score was associated with dementia with a hazard ratio of 1.5 for every point increase in atrophy score ($p < 0.001$), and a hazard ratio of 3.1 for the presence of atrophy based on the dichotomised atrophy score (score 0 - 1 vs 2 - 4, $p = 0.003$). The predictive accuracy of visually assessed MTA was independent of age, gender, education, Mini Mental State Examination score, Clinical Dementia Rating Sum of Boxes score, verbal delayed recall, the presence of hypertension, depression, the APOE-e4 allele and WMH.

The second question was addressed in chapters 3 to 7.

Chapter 3

In chapter 3, the relation between blood pressure and hippocampal atrophy was assessed in a longitudinal, population based study of Japanese American men (the HAAS). Those never treated with anti-hypertensive medication had a significantly increased risk for hippocampal atrophy (OR = 1.7). The non-treated subjects with a systolic blood pressure > 140 mmHg at midlife had an increased risk (OR = 1.98) for hippocampal atrophy. Results were similar for untreated men with a diastolic blood pressure > 90 mmHg at midlife (OR = 3.51). In the analyses, we accounted for potential socio-demographic and clinical confounders. These variables did not change the found associations.

Chapter 4

In chapter 4, the association between blood pressure and MTA was assessed in subjects with AD, referred to an outpatient clinic. In a linear regression analyses, an association was found between pulse pressure ($\beta = 0.08$ per 10 mmHg) and systolic blood pressure ($\beta = 0.05$ per 10

mmHg) and medial temporal lobe atrophy. These associations were particularly found in subjects with WMH, and in subjects with a senile onset of AD.

Chapter 5

In chapter 5, sequential MRIs of 35 subjects with AD from the same outpatient clinic population were assessed. MTA and WMH were determined visually. WMH were classified subcortical (SCWMH) or periventricular (PVWMH). The mean MTA progression after a mean follow-up of 2.2 years was 0.8 for subjects with PVWMH and 0.3 for patients without PVWMH at baseline. Subjects with PVWMH at baseline and those with PVWMH-progression during follow up had a higher risk for MTA and for progression of MTA. This was not found for SCWML.

Chapter 6

In the HAAS, MRI of the brain of subjects with DM were described (chapter 6), with the hypothesis that DM leads to both vascular and neurodegenerative changes. The abnormalities were compared to the MRI of the brains of those with glucose intolerance and those with normal glucose levels. Subjects with DM had more lacunes, smaller hippocampi and more generalized atrophy. The risk for both lacunes and small hippocampi was twice as high in subjects with DM compared to subjects without DM.

Chapter 7

In chapter 7, the association of blood pressure and DM with MTA was sought in a large group of non-disabled subjects with a wide range of WMH, who visited an outpatient clinic for several reasons. Of the subjects, 15% had DM, and 70% had a history of hypertension. Subjects with DM had a significantly raised odds ratio for MTA. Systolic and diastolic blood pressure and a history of hypertension were not associated with MTA There was no interaction between DM and hypertension. Stratification on WMH did not alter the associations.

General discussion

MTA and MCI

In the past decade many studies have addressed the issue of MCI, its heterogeneity, and its value as being a risk state for dementia. Conflicting results are jeopardizing the longevity of the concept of MCI and basically it still exists because of a lack of reliable biological markers for AD.

MCI as such is nothing more than a description of a state with mild cognitive disturbances, usually forgetfulness.[1] The importance of identifying this syndrome is mainly that it can be an early expression of dementia, although studies suggest that up to 40% may never progress to dementia.[2] On the other hand recognizing those patients that will ultimately fulfill criteria for dementia is of utmost importance as soon as treatments become available that may influence the rate of progression or stop even the occurrence of full blown dementia syndrome. This is currently not possible, but without proper markers these drugs can also not be developed.

A first attempt to tackle these questions has been made by investigators looking into the value of hippocampal atrophy on MRI as a predictor of incipient (present) AD.[3-7] We have added to that part of the literature the notion that using even a simple visual grading system, the presence of hippocampal atrophy triples the chance of developing dementia after 3 years. Other studies confirm our finding.[3-8]

For clinical trials the MTA score can be used as an inclusion criterion, as the proportion of subjects who will convert to dementia should be high. In clinical practice, the MTA score is not a sensitive enough marker to use in predicting dementia in the individual, with a sensitivity of 70%, a specificity of 68%, and a PPV of 68% and a NPV of 70%. This means persons with other than (future) AD also have MTA. Therefore, caution should be taken with the interpretation of the score in the individual. Another reason for this prudence is that in old age hippocampal volume diminishes.[9-14] Maybe the cut-off score for pathology should be higher above a certain age, as was recently suggested in a study showing that hippocampal volume loss is independently affected by aging and AD.[15] Another “false-positive” high atrophy score could be caused by hippocampal sclerosis. Sometimes this can be suspected on the basis of a higher signal-intensity of the hippocampus on MRI on the proper sequence, but usually it is found only on histopathology.

In the last few years, the emphasis in MCI is to create subgroups on the basis of cognitive performance.[16] There are 4 potential subgroups: only memory impaired; one domain not-memory impaired; multiple domains including memory impaired; multiple domains non-memory impaired. It is likely that these subgroups have a different prognosis, and that the memory-impaired subgroups are better predictors of AD, but this is in part because memory is used to diagnose AD. Future studies will clarify the clinical and scientific value of the subgroups. It would be interesting to determine the role of the MTA score in predicting dementia and AD in these subgroups.

Vascular risk factors and hippocampal atrophy

The cause of hippocampal atrophy in aging and AD is probably different. Currently, most studies suggest that in aging the number of neurons in the hippocampus does not diminish, but the neurons probably shrink, thus causing a smaller volume. Also reduction of white matter in the hippocampus might attribute to the volume-loss.[17-19] In neuropathological studies in AD, NFT and NP are pathognomic for AD and thought to be caused by neurodegeneration. Neuronal loss is particularly found in the CA1 area and the subiculum.[17,19,20] In this thesis, high blood pressure and DM are found to be associated with hippocampal atrophy, measured either as volume or visually rated, and in subjects with AD as well as in non-demented subjects.

Blood pressure and hippocampal atrophy

High diastolic and systolic blood pressure at midlife increased the risk on hippocampal atrophy for those not treated with anti-hypertensive medication (OR 3.5 and 2). In the LADIS-study, we could not find an increased risk of high blood pressure for hippocampal atrophy; and treatment did not have a modifying effect. The presence or absence of other vascular risk factors, vascular co-morbidity or vascular damage on MRI did not change the findings in these studies. In subjects with AD, however, an association was found between pulse pressure and systolic blood pressure and MTA: for every 10 mmHg increase in pulse-pressure, the MTA score increased with 0.08 points, and for every 10 mmHg increase in systolic blood pressure, the MTA score increased with 0.05. Because this effect is small, it is debatable whether these findings are clinically relevant.

It has been shown many years ago that subjects with hypertension have more NFT and NP in the hippocampus compared to normotensive subjects.[21] More recently, a non-significant reduced hippocampal volume was found in hypertensive subjects.[22] In studies with genetically manipulated hypertensive rats,[23,24] the hippocampus is atrophied and contains NFT and NP. Treatment with anti-hypertensive drugs has a favourable effect on these parameters. In the Rotterdam study[25] subjects with high diastolic blood pressure, not treated with anti-hypertensive drugs, had smaller hippocampi. In this study, the follow up was 5 years and the age of the subjects 60-90 years.

Taken together, it is likely that high blood pressure, particularly if not well-controlled, has a negative influence on hippocampal volume, but the effect size is not large. The reason for not finding robust outcomes in the studies in this thesis might be selection bias. In the HAAS, a longitudinal cohort study, all subjects were old. Hypertensive subjects with vascular complications, who are likely to die younger, were not included, leaving the relatively more healthy subjects in the study. Because of migration, non-participation and death, selection could be an issue. There also might be other confounders or effect-modificators that were not accounted for, however, based on existing literature no important variables were missed. In the LADIS study subjects were younger, but the results presented from this study were cross-sectional. So, the long-term effect of blood pressure on hippocampal volume could not be assessed and causal relations could not be determined. Moreover, the subjects were not demented at baseline, thus causing a small range in hippocampal volume. In AD subjects, it is known that blood pressure drops with dementia severity.

The issues mentioned above most likely underestimate the associations we found.

The role of WMH

High blood pressure is associated with WMH.[26-28] In the Rotterdam study,[26] subjects with high blood pressure, and particularly those with long standing hypertension and those with poor medication control, had a very high relative risk for WMH. In a sample with independently living elderly in Los Angeles,[28] an even small raise in blood pressure over 5 years was associated with more extensive subcortical lesions. Moreover, in the PROGRESS study[27] the same association was found, and subjects treated for hypertension had less progression of the WMH.

In theory, WMH could be an intermediate in the relation between high blood pressure and hippocampal atrophy. WMH could interrupt the neuronal tracts projecting to the hippocampus, causing Wallerian degeneration, and thus causing hippocampal atrophy. The study of Bozzali,[29] with data from diffusion tensor-MRI, even suggests that WMH in AD are likely to be secondary to Wallerian degeneration of fiber tracts due to neuronal loss in cortical associative areas. In the HAAS and LADIS we did not find a modifying effect of WMH on the association between blood pressure and hippocampal atrophy. In subjects with AD, however, the association of high blood pressure and MTA was especially found in subjects with WMH. Also, the presence and progression of PVWMH was associated with MTA and MTA-progression in subjects with AD.

The apparent discrepancy between (mainly) non-demented subjects and subjects with AD is interesting. It suggests that, in AD, WMH might have a negative effect on hippocampal volume, presumably though Wallerian degeneration. In non-demented subjects, however, a different aetiology could be present. The CA1 area of the hippocampus is known to be very sensitive to ischemia.[30,31] High blood pressure causes atherosclerosis and subsequently could cause an impaired cerebral blood flow to the CA1 area, ultimately resulting in atrophy. This same mechanism is, however, suggested in AD. In 2000, de la Torre[32] proposed the hypothesis that advanced aging in the presence of vascular risk factor for AD will converge to create a 'Critically Attained Threshold of Cerebral Hypoperfusion' (CATCH) that will subsequently affect the microcirculation and delivery of energy substrates required for optimal brain cell function.

Another explanation for the association between blood pressure and hippocampal atrophy is a common agent affecting both separately. Such a common factor could be vasopressin, angiotensin converting enzyme, or genetic factors (for review, see Launer[33]).

Diabetes mellitus and hippocampal atrophy

Several studies have investigated the association between DM and cognitive impairment and dementia, including AD, yielding conflicting results. Recently, a review of population-based studies on this subject was published, concluding that subjects with DM have an increased risk for dementia, likely including both vascular dementia and AD.[34] In 1999[35] and in 2004[36] reviews were published about the studies known to date, and the authors came to the same conclusion. Several potential mechanisms have been proposed. In animal studies, it has been shown that tasks, dependent on hippocampal function, are performed worse in hyperglycemia,

although not all studies confirm this effect (for review, see Messier[37]). Chronic hyperglycemia can affect the efficient transport of nutrients like glucose across the blood brain barrier.[38] In situations with stress, when cortisol levels increase, the hippocampus of diabetic rats is extensively damaged in 1/3 the time compared to the hippocampus of non-DM rats.[39]

In hyperglycemia other metabolic processes in DM could directly or indirectly lead to AD-pathology like NP and NFT. For example, advanced glycated end products can accumulate in and cause damage to vascular tissue,[38] are found to be present in NFT and senile plaques,[40,41] and are potent neurotoxins. Also, hyperglycemia could lead to microangiopathy, causing ischemic damage to the hippocampus, the CA1 area in particular.

Insulin degrading enzyme (IDE) degrades insuline and β-amyloid, with a preference for insulin. In DM, IDE is dysfunctioning, thus causing high levels β-amyloid, which can accumulate into senile plaques.[42] Hyperinsulinemia is more prevalent in AD, and the activity of IDE in the hippocampus is diminished in AD, both causing higher levels of β-amyloid.[43,44]

Insulin itself may play an important role. Cerebral insulin signalling is altered in DM. Recently, it was found that insulin evokes tau-phosphorylation, especially in the hippocampus and hypothalamus.[45] Other reports have shown that insulin stimulates β-amyloid secretion, and inhibits the extracellular degradation of β-amyloid by competition of insulin degrading enzyme.[46]

In this respect, it is interesting to mention two hypotheses about the underlying mechanisms of the association of DM and AD. In 2001, Brownlee[47] suggested that chronic hyperglycemia is toxic, either to hippocampal neurons by forming superoxides through metabolism of the increased intracellular glucose, or to microvascular endothelial cells, by impairing the blood brain barrier and thus impairing the transport of glucose. Recently, Convit[39] proposed a different model. His theory holds that as insulin resistance influence the blood brain barrier for transport of glucose to neurons, and increased cortisol has a negative effect on the transport of glucose to the hippocampal neurons, both lead to functional hypoglycaemia, causing damage to the hippocampus and thus causing cognitive deficits.

These hypotheses and the previous data suggest that in DM and possibly also in subjects with IGT the hippocampus might be damaged more severely compared to non-DM subjects.

In this thesis, we investigated the association of DM and hippocampal atrophy in several populations. In the studies on subjects with AD, the number of subjects with DM was too small to investigate this association. Both in the HAAS and the LADIS, an association was found between DM and hippocampal atrophy, although the effect size was not large. However, the same limitations apply as for the blood pressure findings (see previous section).

Therefore, the results could be an underestimation of reality. A support for this is the fact that subjects with DM using insulin, having a longer duration of disease or having disease-related complications, had more hippocampal atrophy. Another shortcoming of the presented studies is that we did not have a good measure of long-term glucose control, like glycosylated haemoglobin A1c.

Diabetes and hypertension

Earlier studies have found an interaction between DM and hypertension: DM was associated with cortical atrophy[48] and dementia,[49,50] particularly in the presence of high blood pressure. In the HAAS, there was no difference in blood pressure between DM, IGT and non-DM, and in the regression models SBP did not alter the found associations between DM and hippocampal atrophy. In the LADIS, no interaction was found between DM and hypertension. As hypertension, particularly not well controlled, was found to be associated with hippocampal atrophy (this thesis),[25] the blood pressure is a variable that should be accounted for. It is possible that hypertension and DM both have an (additional or synergistic) effect on the blood brain barrier or on neurodegeneration, thus causing hippocampal atrophy. Future studies should explore these options.

Another possibility is that DM and AD share common (genetic) factors, which facilitate both processes. One of them could be APOE e4: Peila et al[51] showed that DM, particularly in the presence of the APOE ε4, is associated to AD. Also more NFT and cerebral amyloid angiopathy was found in subjects with APOE e4 allele. In the HAAS (chapter 6), we included the APOE status in the analyses, and did not find a change in the associations.

Suggestions for further studies

MCI and hippocampal atrophy

To further explore the role of hippocampal atrophy in the prediction of dementia, it would be interesting to perform a large prospective study on subjects with MCI, and to subdivide this sample in memory and non-memory, single and multiple domain MCI, according to Petersen.[16] At baseline, sociodemographic data like age, education and race, medical data like history and medication, neuropsychological tests and a neuropsychiatric questionnaire, APOE genotype, cerebrospinal fluid (tau, abeta) and MRI of the brain (MTA, hippocampal volume, WMH, lacunes, infarcts) should ideally be performed or determined. Follow up should be as long as possible, preferably 6 to 10 years, or until a definite diagnose of dementia and cause of dementia is established. The main outcome should be the predicitive effect of hippocampal atrophy and MTA on dementia, with determination of the cause of dementia. Secondary analyses could be performed to determine the predictive value on dementia of other variables, like progression of hippocampal atrophy over time, memory function at baseline and memory decline, and baseline cerebrospinal fluid-markers. Therefore, some diagnostic test, like MRI and neuropsychological tests, should be repeated during the follow up, maybe every 1-2 year. Additionally, it would be interesting to compare the visual and volumetric measures of the hippocampus, as an extra validation for the visual score in a large group of subjects, and to determine the predictive value for dementia of both measures. As vascular risk factors like hypertension and DM have an influence on hippocampal volume and dementia, but also on other vascular damage in the brain, and because vascular dementia is based on vascular damage, the influence of lacunes, infarcts and WMH should be determined on the outcome of dementia. Then it should be possible to validate the subgroups of MCI, and a more useful prediction for future patients is possible. These subgroups could be a better basis for (farmacological) therapy.

Risk factors for hippocampal atrophy

To further explore risk factors for hippocampal atrophy, it is necessary to conduct a large, population-based, prospective study, with a follow up from midlife (40-50 years) until death. The subjects should be a mixture of men and women, several races and social backgrounds. A wide number of socio-demographic data should be collected, as well as the medical history,

medication and hospital records. MRI of the brain (hippocampal volume, WMH, infarcts, atrophy), neuropsychological investigations and preferably cerebrospinal fluid should be collected at baseline and after that every five year. Pathological confirmation on diagnoses made during life, particularly dementia, should be made. Such as study will need to include a substantial number of subjects with vascular risk factors. It would be interesting to evaluate the effect on hippocampal volume of a stricter handling of blood glucose and blood pressure. Therefore, for these subjects, more regular control of blood pressure and glucose, HbA1c, should be performed.

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Samenvatting

De ziekte van Alzheimer (AD) is een veel voorkomende oorzaak van dementie, waarvan de diagnose wordt gesteld aan de hand van klinische criteria. AD wordt tevens gekenmerkt door hippocampus atrofie. De hippocampus is een onderdeel van de mediale temporaal kwab. Atrofie van de mediale temporaal kwab kan beoordeeld worden met een visuele beoordelingsschaal, de mediale temporal kwab atrofie (MTA)-schaal volgens Scheltens. Het volume van de hippocampus kan met volume-metingen op de MRI-scan bepaald worden.
Bij mild cognitive impairment (MCI) is er sprake van een cognitieve stoornis in (soms meer dan) één domein, waarbij de activiteiten van het dagelijks leven intact zijn. Wanneer dit domein het geheugen is, is er sprake van amnestische MCI. Dit kan een eerste klinische uiting zijn van AD. Het is van belang de subgroep van mensen met MCI die dement gaat worden, te kunnen onderscheiden van de mensen met MCI die niet dement worden, onder andere vanwege toekomstige therapiën en wetenschappelijke/farmaceutisch onderzoek. Mogelijk is hippocampus atrofie hiervoor een goede voorspeller.

In **hoofdstuk 2** worden 75 patiënten met MCI beschreven die een MRI scan ondergaan. Hierop wordt de MTA-score bepaald. Na een gemiddelde periode van 34 maanden was 49% dement geworden. De MTA score had een hazard ratio voor dementie van 1,5 voor elk punt toename in atrofie ($p < 0,001$), en een hazard ratio van 3,1 voor atrofie gebaseerd op een gedichotomoseerde score (score 0-1 vs 2-4, $p = 0,003$). Deze resultaten zijn onafhankelijk van leeftijd, geslacht, opleiding, cognitie-maten (Clinical Dementia Rating schaal, Mini Mental State Examination en verbale uitgestelde recall), hypertensie, depressie, het ApoE epsilon4 allel en witte stof hyperintensiteiten op de MRI.

Hippocampus atrofie bij dementie, vooral AD, wordt gewoonlijk beschouwd als het gevolg van neurodegeneratie, waarbij beta-amyloid zich ophoopt tot seniele plaques en het tau-eiwit hyperfosforyleert en neurofibrillaire tangles vormt. Uit epidemiologisch onderzoek is naar voren gekomen dat vasculaire risicofactoren, zoals hypertensie en diabetes mellitus (DM), een risicofactor zijn voor dementie, zowel vasculaire dementie als AD. Ook komen er bij AD vaak vasculaire leasies voor op de MRI scan. Al langer is bekend dat een deel van de hippocampus gevoelig is voor ischemie.

Hieruit volgt onze hypothese dat vasculaire risicofactoren een invloed zouden kunnen hebben op het hippocampus volume. In de hoofdstukkken 3 tot en met 7 wordt deze hypothese getest in verschillende populaties.

In **hoofdstuk 3** is de relatie tussen bloeddruk en hippocampus atrofie onderzocht in een longitudinaal, populatie onderzoek onder Japans-Amerikaanse mannen (de Honolulu Asian Aging Study (HAAS)). Degenen die niet behandeld werden met anti-hypertensiva hadden een significant verhoogd risico op hippocampus atrofie (odds ratio (OR) = 1,7). Degenen met een hoge systolische bloeddruk (> 140 mmHg) gedurende middelbare leeftijd die niet behandeld werden met anti-hypertensiva, hadden een verhoogd risico op hippocampus atrofie op oudere leeftijd (OR = 1,98), evenals degenen met een verhoogde diastolische bloeddruk (> 90 mmHg) op middelbare leeftijd zonder anti-hypertensiva gebruik (OR = 3,51). Bij de analyses werd rekening gehouden met potentiële socio-demografische en klinische verstorende factoren. Deze variabelen veranderden de uitkomst van het onderzoek niet.
In **hoofdstuk 4** wordt de relatie tussen bloeddruk en MTA beschreven bij 159 mensen met AD. Met lineaire regressie werd een verband gevonden tussen polsdruk (het verschil tussen systolisch en diastolische bloeddruk) en MTA (β = 0,08 per 10 mmHg, dit betekent dat per 10 mmHg stijging in de polsdruk de MTA score 0,08 toeneemt), en systolische bloeddruk en MTA (β = 0,05 per 10 mmHg). Deze associaties werden vooral gevonden in degenen met een seniele AD, en in degenen met witte stof hyperintensiteiten op de MRI-scan.
In **hoofdstuk 5** gekeken naar de progressie van de witte stofafwijkingen en MTA op MRI met behulp van seriële MRI-scans bij 35 mensen met AD. Subcorticale en periventriculaire witte stof hyperintensiteiten (SCWMH en PVWMH) en MTA werden visueel beoordeeld op de eerste en tweede MRI-scan. Na gemiddeld 2,2 jaar was de progressie in MTA 0,8 voor ptn met PVWMH en 0,3 voor degenen zonder PVWMH tijdens de eerste MRI-scan. Degenen met PVWMH op de eerste MRI-scan en degenen met PVWMH progressie hadden een hogere kans op MTA en MTA-progressie. Voor SCWMH werden geen verschillen gevonden.
In **hoofdstuk 6** wordt de hypothese getoetst of DM zowel degeneratieve als vasculaire afwijkingen in de hersenen kan veroorzaken. In de HAAS werden de MRI-scans van Japans-Amerikaanse mannen met DM vergeleken met MRI-scans van mannen met glucose-intolerantie, die een hoog risico hebben op DM, en van mannen met een normaal (veneus) glucose gehalte. Mannen met DM hadden meer lacunes, kleinere hippocampi en meer gegeneraliseerde atrofie. Het risico op lacunes en een kleine hippocampus was 2 maal zo groot voor degenen met DM vergeleken met degenen zonder DM. Degenen met glucose-

intolerantie hadden dezelfde kans op lacunes, infarcten, witte stof hyperintensiteiten en een kleine hippocampus als degenen met een normaal glucose.
In **hoofdstuk 7** is het verband tussen DM en bloeddruk met MTA onderzocht in een grote groep mensen met een verschillende ernst van witte stof hyperintensiteiten op de MRI-scan. Zij bezochten een polikliniek om verschillenden redenen maar functioneerden zelfstandig en waren niet dement. Participanten maakten deel uit van de LeukoAraiosis and Disability Study (LADIS). 15% van de mensen had DM, 70% had de diagnose hypertensie. Mensen met DM hadden een verhoogd risico op MTA (MTA score 3 (ernstige atrofie): OR = 2.9 (95% CI = 1.1 – 7.8), MTA score 2 (matige atrofie): OR = 1.8 (95% CI = 0.9 – 4), vergeleken met MTA score of 0 (= geen atrofie)). Systolische en diastolische bloeddruk en een diagnose hypertensie waren niet gerelateerd aan MTA. Er was geen interactie tussen DM en hypertensie. De ernst van de witte stof hyperintensiteiten had geen invloed op de uitkomst.

Op basis van dit proefschrift kan ten eerste geconcludeerd worden dat MTA een goede voorspeller is voor dementie in mensen met MCI. MTA kan een nuttig middel kan zijn voor het selecteren van patienten voor wetenschappelijk onderzoek. Ook in de klinische praktijk is het een makkelijk toepasbaar middel bij de screening van mensen met milde cognitieve stoornissen, alhoewel de MTA score niet sensitief genoeg is om een zekere uitspraak te doen over het verdere ziekte-beloop in een individueel geval.

Ten tweede volgt uit de andere hoofdstukken dat DM en hypertensie een negatieve invloed hebben op het hippocampus volume. Deze associaties zijn verschillend van sterkte en significantie in de verschillende populaties. Tevens is er een effect van (anti-hypertensive en anti-diabetische) medicatie en de aanwezigheid witte stof hyperintensiteiten op deze associaties. In **hoofdstuk 8** wordt hierop ingegaan en worden de mogelijke onderliggende pathologische processen belicht.

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Curriculum vitae

De auteur werd op 5 maart 1970 geboren in Zaandijk, gemeente Zaandam, als oudste van een gezin met 4 kinderen. Na een aantal jaren in IJmuiden te hebben gewoond, is het gezin naar Heemskerk verhuisd, waar de auteur op de kleuterschool en basisschool heeft gezeten. Daarna werd het Gymnasium met goed gevolg doorlopen op het PIUS X college te Beverwijk. Van 1988 tot 1995 heeft de auteur geneeskunde gestudeerd aan de Vrije Universiteit te Amsterdam. In 1991 is zij getrouwd met Herman Pelgrim, en in april 1996 is Anne geboren. Vanaf augustus 1996 is de auteur een jaar lang AGNIO neurologie geweest in het Spaarne ziekenhuis te Haarlem. Vervolgens is zij 2 jaar AGNIO neurochirurgie geweest in het VUmc te Amsterdam. In deze periode, in september 1998, is Bram geboren. Vanaf september 1999 tot december 2002 heeft de auteur gewerkt als arts-onderzoeker bij het Alzheimer centrum aan het VUmc, wat tot deze promotie heeft geleid. In deze periode heeft ze 6 maanden voor het NIA/NIH in Bethesda, USA, gewerkt, waar ze volumes van hippocampi heeft gemeten in het kader van de Honolulu Asia Aging Study. Vanaf december 2002 is de auteur in opleiding tot neuroloog, en zij hoopt dit in juni 2008 af te ronden.

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